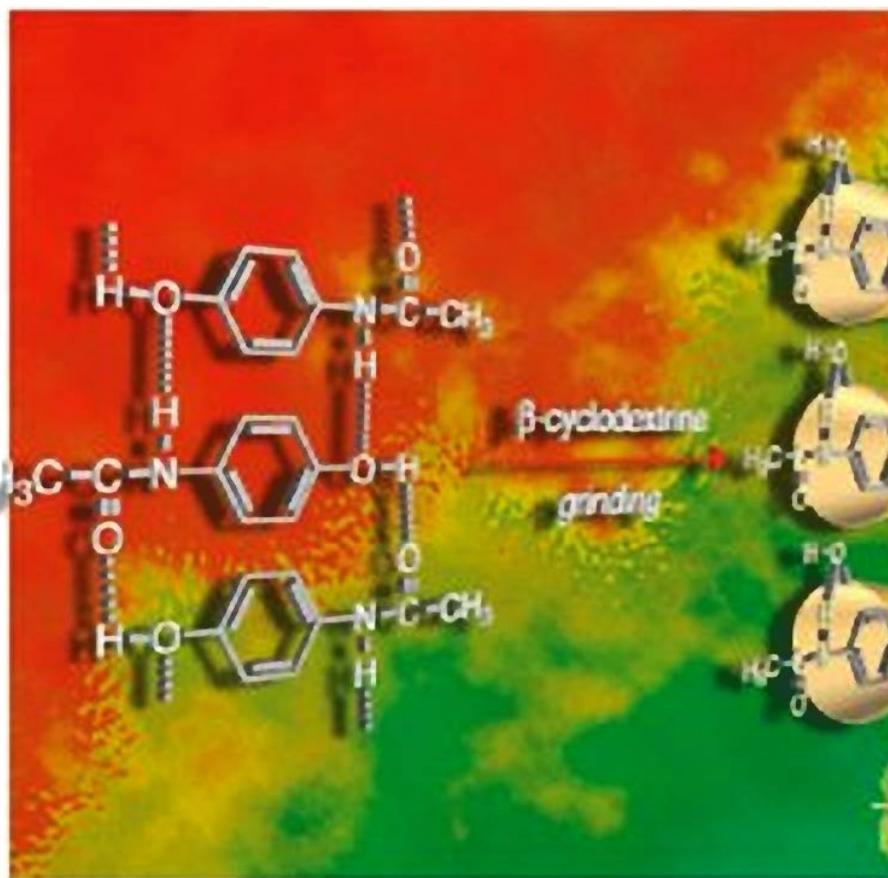


Solvent-free Organic Synthesis

Second, Completely Revised and Updated Edition

With a Foreword by Gerd Kaupp



Koichi Tanaka

Solvent-free Organic Synthesis

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Koichi Tanaka

Solvent-free Organic Synthesis

2nd Completely Revised and Updated Edition

With a Foreword by Gerd Kaupp



WILEY-VCH Verlag GmbH & Co. KGaA

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Foreword

Waste prevention and environmental protection are the major requirements in an overcrowded world of increasing demands. Synthetic chemistry continues to develop various techniques for obtaining better products with less environmental impact. One of the more promising approaches is solvent-free organic synthesis. The book of Koichi Tanaka collects recent examples in this field in a concise way so that their performance and merits can be easily judged. This endeavor is very welcome, as most recent syntheses and educational textbooks largely neglect solvent-free techniques. These views are nicely supported by the high impact of the book that appears now in the second edition, six years after the first one. The book is completely revised and updated with more than 200 reactions that have been published since the appearance of the first edition. It was a good decision to leave out the entire subchapters on microwave-assisted reactions that are not really solvent-free if they require preconditioning of the reactants by dissolution in a solvent with auxiliaries followed by evaporation prior to the heating in the reactor, and if many of these examples actually proceed exothermally without auxiliaries and without heating. This also provides the space for new chapters on Solvent-free Polymerization and Supramolecular Complexation.

The field of solvent-free organic synthesis covers various techniques in all branches of organic chemistry. It includes stoichiometric solid–solid reactions and gas–solid reactions without auxiliaries yielding single products in pure form that do not require solvent-consuming purification steps after the actual reaction. It also includes some stoichiometric melt reactions that occur without auxiliaries and with quantitative yield due to direct crystallization of the product. Although such reactions are by far the best choice for applications of solvent-free chemistry with excellent atom economy, the advantages of avoiding solvents should not be restricted to them. Solvent-free liquid phase reactions, without direct crystallization, that do not provide 100% yield of one product can be profitably applied when unfavorable crystal packing and low melting points impede solid-state reaction. However, solvents are required for purification in these cases, which detracts from atom economy. The higher concentration of reactants in the absence of solvents leads to more favorable kinetics than in solution. Most solvent-free reactions run to completion and proceed at room temperature or slightly above; others require cooling to lower temperatures. Auxiliaries such as catalysts or solid supports are rarely required. If such a catalyst is a liquid or if “only a little solvent” is added, this is no longer solvent-free in a strict sense. Moreover, reactions with liquid products that continuously dilute the reaction mixtures are at best borderline cases that should, however, be accepted here since no auxiliary solvent is involved. The attitude implied in many current publications extends the term “solvent-free” to the application of solid or liquid reagents with up to 10% excess of one of them (rather than the required precise stoichiometry) and/or less than 10% of a liquid or soluble catalyst. Furthermore, it seems widely accepted in the field that solvent used for purification and isolation of the products is not counted in “solvent-free” syntheses. On the other hand, photolysis of insol-

uble solids in (usually aqueous) suspensions undoubtedly qualifies for inclusion as a solvent-free technique, but not the taking up of reagents from a liquid for reaction with a suspended solid.

Reacting gases that can be evaporated may be in excess if they do not condense to liquid phases, but reactions in supercritical media are clearly not the subject of solvent-free chemistry and deserve their own treatment. For practical reasons, this book does not deal with homogeneous or contact-catalyzed gas-phase reactions. Furthermore, protonations, solvations, simple complexations, racemizations and other stereoisomerizations are not covered, in order to concentrate on more complex chemical conversions. This strategy allowed the presentation of diverse reaction types and techniques, including those that proceed only in the absence of liquid phases, in one convenient volume.

Fortunately, solvent-free reactions are scalable, and the reports that did indeed perform the scale-up beyond the mg or gram scale have been emphasized. Quantitative yield without the requirement for solvent consuming work-up also on the large-scale is the ultimate goal and the book collects many examples that perform or promise to perform properly. Therefore, this valuable compilation will become a useful resource for the development of improved sustainable syntheses in industry and academia with the aims of avoiding catalysts and saving resources wherever possible and of preventing all the waste that is produced by using auxiliaries and by unnecessarily creating nonuniform reactions with less than 100% yield. This clearly designed and structured book on solvent-free organic synthesis will be of great value for the broader application of better synthetic techniques and thus for a better environment.

October 2008

Gerd Kaupp
University of Oldenburg

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Preface to the Second Edition

Since the first edition of this book appeared in 2003, the field of solvent-free organic synthesis has undergone an explosion in research and I have received considerable response from readers. With the aid of this information I have completely updated this book. In this second edition, over 200 examples of new solvent-free organic reactions, published in the journals during 2003 to 2007, have been added. The most obvious changes in this book are the two new chapters: one on polymerization (Chapter 14) and the other on supramolecular complexation (Chapter 15). Additionally, all the sections on solvent-free reactions under microwave irradiation have been deleted, since Professor A. Loupy covers this area in his book on Microwaves in Organic Synthesis (Wiley-VCH, 2006).

I hope that this second edition will be of value to all scientists and engineers, in both academia and industry, who are concerned with green and sustainable chemistry.

Koichi Tanaka
Kansai University

Preface to the First Edition

The elimination of volatile organic solvents in organic syntheses is a most important goal in ‘green’ chemistry. Solvent-free organic reactions make syntheses simpler, save energy, and prevent solvent wastes, hazards, and toxicity.

The development of solvent-free organic synthetic methods has thus become an important and popular research area. Reports on solvent-free reactions between solids, between gases and solids, between solids and liquid, between liquids, and on solid inorganic supports have become increasingly frequent in recent years.

This volume is a compilation of solvent-free organic reactions, covering important papers published during the past two decades. It contains graphical summaries of 537 examples of solvent-free organic reactions and is divided into 14 chapters:

1. Reduction,
2. Oxidation,
3. Carbon–Carbon Bond Formation,
4. Carbon–Nitrogen Bond Formation,
5. Carbon–Oxygen Bond Formation,
6. Carbon–Sulfur Bond Formation,
7. Carbon–Phosphorus Bond Formation,
8. Carbon–Halogen Bond Formation,
9. Nitrogen–Nitrogen Bond Formation,
10. Rearrangement,
11. Elimination,
12. Hydrolysis,
13. Protection,
14. Deprotection.

Each summary includes a structure scheme, an outline of the experimental procedure, and references to help the reader.

I hope that this volume will contribute to the studies of organic chemists in industry and academia and will encourage the pursuit of further research into solvent-free organic synthesis.

Koichi Tanaka
Ehime University

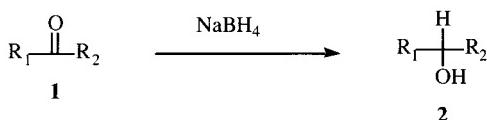
1 Reduction

1.1 Solvent-Free Reduction

Type of reaction: reduction

Reaction condition: solid-state

Keywords: ketone, NaBH₄, alcohol



- a: R₁; R₂ = Ph
- b: R₁=*trans*-PhCH=CH; R₂=Ph
- c: R₁=2-naphthyl ; R₂=Me
- d: R₁=PhCH(OH); R₂=Ph
- e: R₁=PhCH₂; R₂=Ph
- f: R₁, R₂=4-*t*-Bu-cyclohexyl

Experimental procedures:

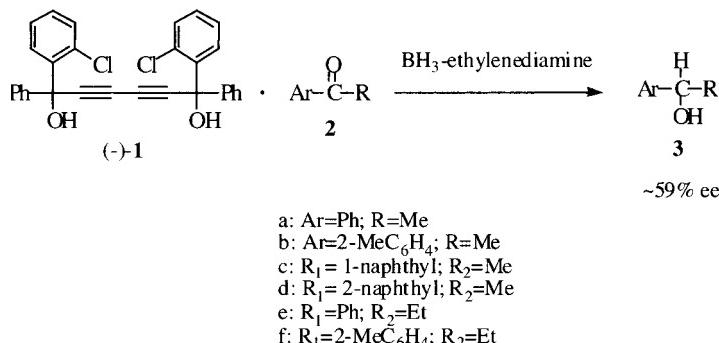
When a mixture of the powdered ketones and a ten-fold molar amount of NaBH₄ was kept in a dry box at room temperature with occasional mixing and grinding using an agate mortar and pestle for 5 days, the corresponding alcohols were obtained in good yields.

References: F. Toda, K. Kiyoshige, M. Yagi, *Angew. Chem. Int. Ed. Engl.*, **28**, 320 (1989).

Type of reaction: reduction

Reaction condition: solid-state

Keywords: ketone, enantioselective reduction, BH₃-ethylenediamin complex, inclusion complex, alcohol

**Experimental procedures:**

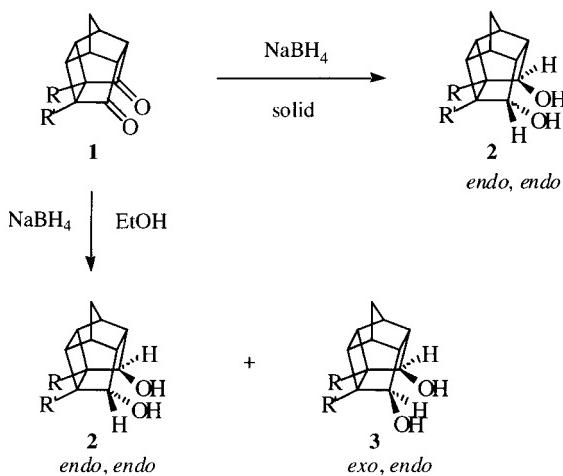
A mixture of finely powdered inclusion complex of $(-)\text{-1}$ with **2** was kept under N₂ at room temperature for 24 h by occasional stirring. The reaction mixture was decomposed with water and extracted with ether. The ether solution was washed with dilute HCl, dried, and evaporated to give crude alcohols. Distillation of the crude alcohols in vacuo gave pure alcohols.

References: F. Toda, K. Mori, *Chem. Commun.*, **1245** (1989).

Type of reaction: reduction

Reaction condition: solid-state

Keywords: cage diketone, sodium borohydride, alcohol



a: R=R'=H; b: R,R'=-CH₂CH₂-; c: R,R'=-CH=CH-

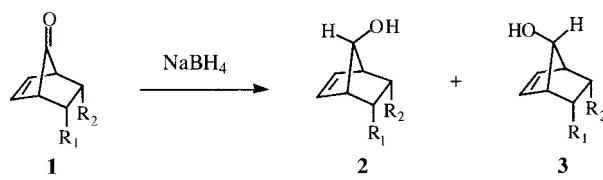
Exerimental procedures:

Cage diketone **1a** (87 mg, 0.50 mmol) and NaBH₄ (400 mg, excess) were ground together under an argon atmosphere into a fine powder, thereby producing an intimate solid mixture. The resulting powdery mixture was agitated under argon at room temperature for 7 days. Water (15 mL) then was added, and the resulting mixture was extracted with CHCl₃ (3×20 mL). The combined extracts were washed with water (30 mL), dried (Na₂SO₄), and filtered, and the filtrate was concentrated in vacuo to afford pure *endo,endo*-diol **2a** (89 mg, 100%) as a colorless microcrystalline solid: mp 275–276°C.

References: A. P. Marchand, G. M. Reddy, *Tetrahedron*, **47**, 6571 (1991).

Type of reaction: reduction**Reaction condition:** solid-state

Keywords: 7-norbornenone, NaBH₄, π -face selectivity, alcohol



- a: R₁=R₂=COOCH₃
- b: R₁=H; R₂=COOCH₃
- c: R₁=H; R₂=CN
- d: R₁=R₂=CH₂OCH₃

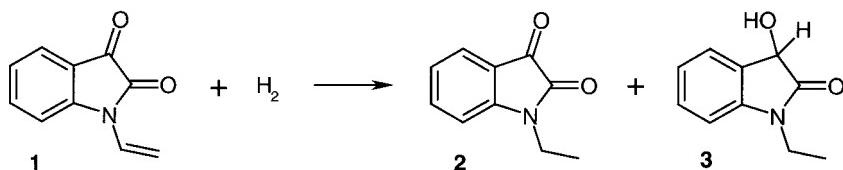
Exerimental procedures:

A mixture of **1a** and NaBH₄ (excess) was fully ground and left aside in a sample vial (1–2 days, sonication reduces the reaction time to a few hours). Usual work-up led to the formation (80%) of **2a** and **3a** in 87:13 ratio.

References: G. Mehta, F. A. Khan, K. A. Lakshmi, *Tetrahedron Lett.*, **33**, 7977 (1992).

Type of reaction: reduction**Reaction condition:** solid-state

Keywords: N-vinylisatin, hydrogenation, gas-solid reaction, *N*-ethyldioxindole, *N*-ethylisatin

**Experimental procedure:**

Powdered crystals of **1** (670 mg, 3.9 mmol) that were recrystallized from *n*-hexane were evacuated in a 1 L flask and heated to 45 °C. Hydrogen gas was fed in from a steel cylinder (1 bar, 45 mmol) and the system kept at 45 °C for 2 days. The crystals changed their appearance and contained 67 mg (10%) unreacted **1**, 502 mg (74%) **2** and 110 mg (16%) **3**. The products were separated by preparative TLC on 200 g SiO₂ with dichloromethane.

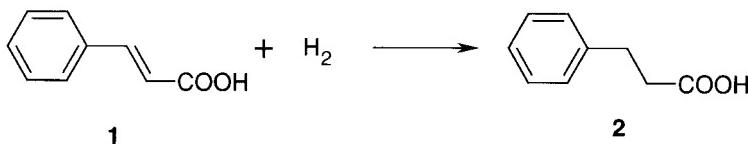
If sublimed **1** was equally treated with H₂, no hydrogenation occurred. Thus, residual Pd impurities from the synthesis of **1** appear to activate the hydrogen in these solid-state reactions.

References: G. Kaupp, D. Matthies, *Chem. Ber.*, **120**, 1897 (1987).

Type of reaction: reduction

Reaction condition: solid-state

Keywords: cinnamic acid, hydrogenation, gas-solid reaction, 3-phenylpropionic acid

**Experimental procedure:**

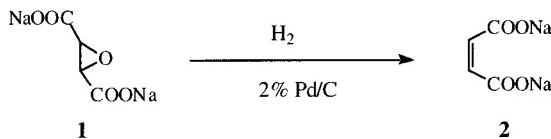
Cinnamic acid crystals **1** were doped by inclusion of some Pd (compound) upon recrystallization from methanol with Na₂[PdCl₄] (10⁻⁴ mol L⁻¹). Such crystals **1** were hydrogenated with excess H₂ at 1 bar and 30 °C for 6 days and yielded 48% of **2**.

References: G. Kaupp, D. Matthies, *Mol. Cryst. Liq. Cryst.*, **161**, 119 (1988).

Type of reaction: reduction

Reaction condition: solid-state

Keywords: epoxide, disodium *trans*-epoxysuccinate, palladium catalyst, disodium malate, alkene

**Experimental procedures:**

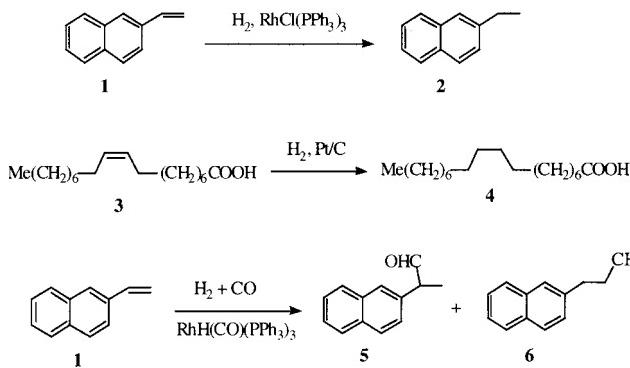
A supported palladium catalyst (0.50 g) was prepared with hydrogen gas at 200 °C for 30 min. The catalyst was mixed with disodium *trans*-epoxysuccinate (0.10 g), and the mixture was ground well with a mortar and pestle at room temperature. The mixture was placed in an autoclave and then shaken in the presence of hydrogen gas (9.0 MPa) at 100 °C for 14 h.

References: T. Kitamura, T. Harada, *J. Mol. Catal.*, **148**, 197 (1999).

Type of reaction: reduction

Reaction condition: solvent-free

Keywords: 2-vinylnaphthalene, hydrogenation, hydroformylation, subcritical CO₂

**Experimental procedures:**

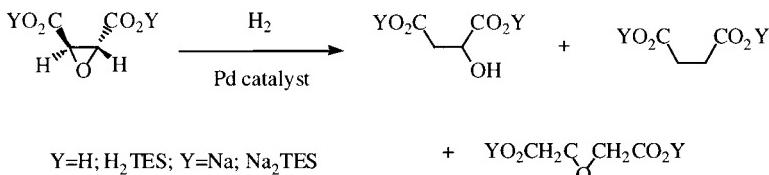
The hydrogenation of vinylnaphthalene **1** was performed by mixing solid chlorotris(triphenylphosphine)rhodium catalyst (7.0 mg, 7.6 μmol) with solid 2-vinyl-naphthalene (350 mg, 2.27 mmol, substrate:Rh=300:1), both fine powders. The mixture was placed, with a stirring bar, into a 22 mm diameter flat-bottomed glass liner in a 160-mL high-pressure vessel, which was then sealed and warmed to 33 °C in a water bath. The vessel was flushed and pressurized with H₂ to 10 bar. This was considered the start of the reaction. Carbon dioxide was then added to a total pressure of 67 bar. After 30 min, the vessel was removed from the water bath and vented. The product mixture was dissolved in CDCl₃ and characterized by ¹H NMR spectroscopy.

References: P. Jessop, D. C. Wynne, S. DeHaai, D. Nakawatase, *Chem. Commun.*, 693 (2000).

Type of reaction: reduction

Reaction condition: solvent-free

Keywords: epoxide, *trans*-epoxysuccinic acid, hydrogenation, hydrogenolysis, alcohol



Experimental procedures:

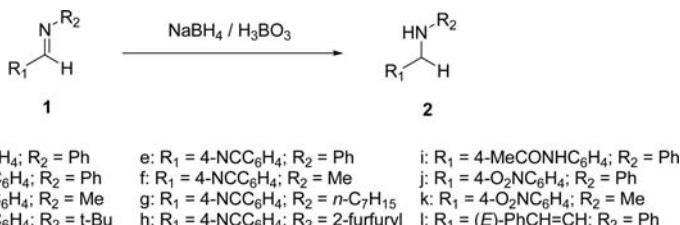
A supported Pd catalyst (0.1 g) was pretreated at 200 °C for 30 min with a H₂ stream. The resulting catalyst was mixed with H₂TES or Na₂TES (0.1 g), and the mixture was ground to a fine powder using a mortar and pestle. The mixture was placed in a Schlenk tube, and then the air in the tube was replaced by hydrogen gas. The reaction vessel was allowed to stand at 30 °C in the pressure of hydrogen (0.1 MPa) for 2 days.

References: T. Kitamura, T. Harada, *Green Chem.*, **3**, 252 (2001).

Type of reaction: reduction

Reaction condition: solvent-free

Keywords: imine, reduction, sodium borohydride



Experimental procedures:

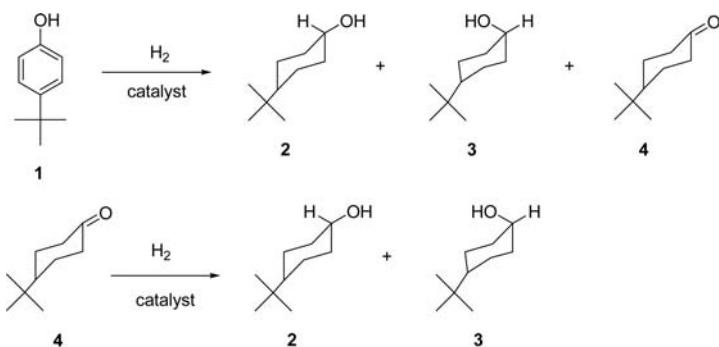
A mixture of imine derivatives **1** (10 mmol), NaBH₄ (10 mmol) and boric acid (10 mmol) was ground with an agate mortar and pestle for 0.5–1.0 h until TLC showed complete disappearance of the starting material. The mixture was quenched with a saturated aqueous solution of NaHCO₃, followed by filtration of the resultant suspension to give product amines **2**. When the product was liquid, it was isolated by extraction with CH₂Cl₂ or Et₂O instead of filtration.

References: B. T. Cho, S. K. Kang, *Synlett*, 1484 (2004).

Type of reaction: reduction

Reaction condition: gas–solid

Keywords: hydrogenation, 4-*tert*-butylphenol



Experimental procedures:

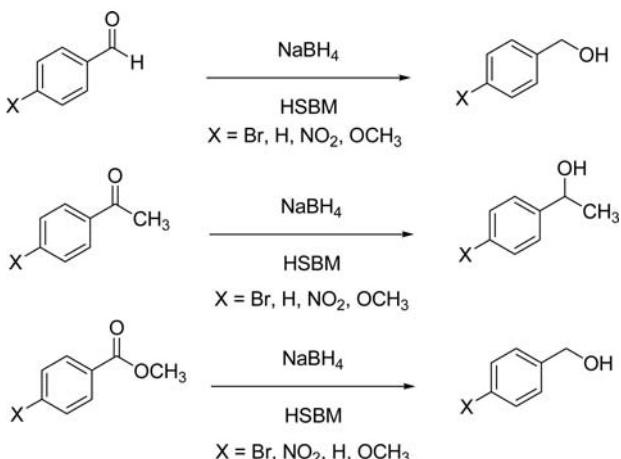
All hydrogenation experiments were carried out at atmospheric pressure in a reactor, consisting of a flask attached to a burette filled with mercury and equipped with stopcocks that permit removal of air before the introduction of hydrogen. The mixed catalyst/solid substrate was placed at the bottom of the flask reactor to form a thin layer (2–3 mm) and then evacuated to approximately 10⁻³ Torr for 10 min. After introducing hydrogen (760 Torr), the reaction was carried out until complete transformation of the solid had occurred; usually the reaction was completed within 18 h. This transformation was accompanied by the formation of thin needles on the surface of the solid catalytic bed, which correspond to the resulting products: *cis*-4-*tert*-butylcyclohexanol, *trans*-4-*tert*-butylcyclohexanol and 4-*tert*-butylcyclohexanone. The reaction mixture was extracted with ethyl ether, and the catalyst separated by simple filtration. Analysis of the products was carried out by gas chromatography and mass spectroscopy.

References: F. Sabra, R. Lamartine, *New J. Chem.*, **16**, 1043 (1992); F. Sabra, R. Lamartine, *New J. Chem.*, **16**, 1049 (1992).

Type of reaction: reduction

Reaction condition: solvent-free

Keywords: reduction, ester, high-speed ball milling

**Experimental procedures:**

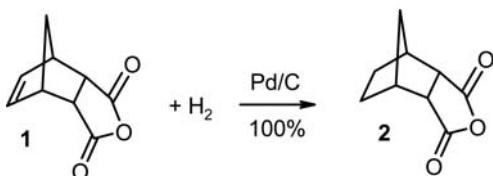
The reactions were conducted in a custom-made 0.5×2.0 in screw-capped stainless steel vial and milled with an 0.250 in aluminum oxide ball-bearing in a Speex certiprep mixer/mill 8000 M for approximately 17 h. Various para-substituted aryl methyl benzoates were reduced using a 5:1 ratio of lithium chloride : sodium borohydride. At the conclusion of the reaction, the products were washed with 10% HCl and the remaining solids were dried over a Hirsch funnel. Liquid products were isolated by extraction from a minimal amount of ethyl acetate.

References: J. Mack, D. Fulmer, S. Stofel, N. Santos, *Green Chem.*, **9**, 1041 (2007).

Type of reaction: reduction

Reaction condition: solid-state

Keywords: large scale, gas-solid reaction, catalytic hydrogenation, norbornene dicarboxylic anhydride, stereospecific

**Experimental procedure:**

A mixture of **1** (200 g, 1.22 mol) and 200 mg Pd/C were milled in a 2-L horizontal stellite rotary ball mill (Simoloyer®) with 2 kg steel balls (100Cr6; 5 mm diameter) at 900 min⁻¹ with water cooling (15 °C) and temperature control (kept

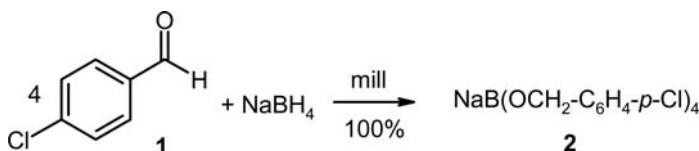
at <40 °C) in an atmosphere of 0.8–1 bar hydrogen with constant gas supply. The gas consumption ceased after 40 min, but milling was continued for a further 20 min. The residual hydrogen (1.5 L) was pumped off and the quantitatively obtained **2** (mp 170 °C) was milled out at 600 min⁻¹ in an air stream through a cyclone. Separation from the catalyst was achieved by vacuum sublimation.

References: G. Kaupp, *Top. Curr. Chem.* **254**, 95 (2005).

Type of reaction: reduction

Reaction condition: solid-solid

Keywords: ball mill, quantitative, aldehyde, tetraalkoxyborate



Experimental procedure:

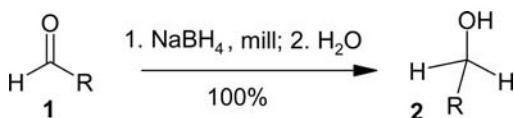
The aldehyde **1** (4.00 mmol) and NaBH₄ (1.00 mmol) were ball-milled at 25 °C for 10 min to obtain sodium tetra-(4-chlorobenzyl)borate **2** quantitatively. This was collected with exclusion of moisture since it is easily hydrolyzed, liberating the 4-chlorobenzyllic alcohol in moist air. Further aldehydes behave correspondingly.

References: M.R. Naimi-Jamal, J. Mokhtari, M.G. Dekamin, G. Kaupp, *Chem. Eur. J.* (2008), submitted.

Type of reaction: reduction

Reaction condition: solid state

Keywords: solid-solid reaction, benzaldehydes, benzylalcohols



- a: $\text{R} = 4\text{-ClC}_6\text{H}_4$; 10 min
- b: $\text{R} = 4\text{-BrC}_6\text{H}_4$; 10 min
- c: $\text{R} = 2\text{-NO}_2\text{C}_6\text{H}_4$; 10 min
- d: $\text{R} = 3\text{-NO}_2\text{C}_6\text{H}_4$; 10 min
- e: $\text{R} = 4\text{-CNC}_6\text{H}_4$; 15 min
- f: $\text{R} = 4\text{-(NMe}_2\text{)C}_6\text{H}_4$; 20 min
- g: $\text{R} = 4\text{-MeOC}_6\text{H}_4$; 15 min
- h: $\text{R} = \text{CH}=\text{CHC}_6\text{H}_5$; 10 min
- i: $\text{R} = 2\text{-thiophenyl}$; 15 min

Experimental procedures:

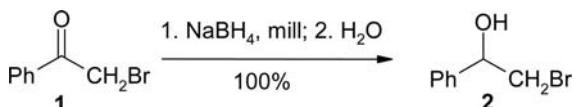
The aldehyde **1** (4.00 mmol) and NaBH_4 (1.00 mmol) were ball-milled at 25 °C for the times given at 25 °C and at 25 min^{-1} . The mixture was quenched with water, followed by filtration of the resultant suspension to give the solid product alcohol. When the product was liquid, it was isolated by extraction with 5 mL CH_2Cl_2 or by distillation.

References: M.R. Naimi-Jamal, J. Mokhtari, M.G. Dekamin, G. Kaupp, *Chem. Eur. J.* (2008), submitted; including further examples.

Type of reaction: reduction

Reaction condition: solid-state

Keywords: solid-solid reaction, phenacylbromide, NaBH_4 , chemoselective



Experimental procedure:

Phenacylbromide **1** (1.00 mmol) and NaBH_4 (0.25 mmol) were ball-milled in a 10-mL vessel at 25 min^{-1} . After 20 min the mixture was quenched with water and extracted with diethyl ether to give *rac*-**2** quantitatively. No side products were observed.

References: M.R. Naimi-Jamal, J. Mokhtari, M.G. Dekamin, G. Kaupp, *Chem. Eur. J.* (2008), submitted.

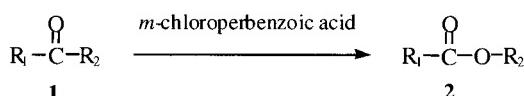
2 Oxidation

2.1 Solvent-Free Oxidation

Type of reaction: oxidation

Reaction condition: solid-state

Keywords: ketone, Baeyer-Villiger reaction, *m*-chloroperbenzoic acid, ester



a: R₁=4-BrC₆H₄; R₂=Me

b: R₁=Ph; R₂=CH₂Ph

c: R₁=R₂=Ph

d: R₁=Ph; R₂=4-MeC₆H₄

e: R₁=Ph; R₂=2-MeC₆H₄

Experimental procedures:

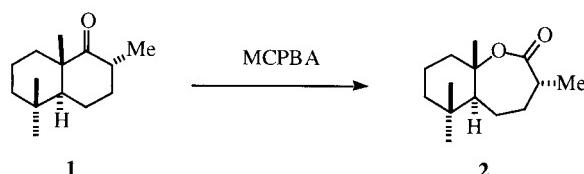
The oxidations were carried out at room temperature with a mixture of powdered ketone and 2 mol equiv. of powdered *m*-chloroperbenzoic acid. When the reaction time was longer than 1 day, the reaction mixture was ground once a day with agate pestle and mortar. The excess of peroxy acid was decomposed with aqueous 20% NaHSO₄, and evaporated. The crude product was chromatographed on silica gel (benzene-CHCl₃).

References: F. Toda, M. Yagi, K. Kiyoshige, *Chem. Commun.*, 958 (1988).

Type of reaction: oxidation

Reaction condition: solid-state

Keywords: decalone, Baeyer-Villiger oxidation, norsesquiterpenoid, lactone



Experimental procedures:

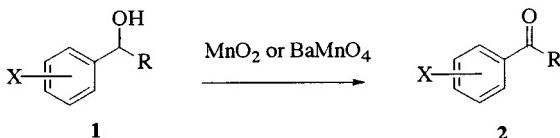
A mixture of the decalone **1** (40.8 mg, 196 µmol) and MCPBA (127 mg, 80%, 589 µmol) was left to stand at room temperature for 8 h and at 60 °C for 12 h. The resulting mixture was diluted with EtOAc and the organic layer was washed with sat. NaHCO₃ (2×), water and brine. Evaporation of the solvent followed by MPLC purification of the residue (EtOAc-n-hexane, 1:10) gave lactone **2** (31.5 mg, 72%) as a colorless oil.

References: H. Hagiwara, H. Nagatome, S. Kazayama, H. Sakai, T. Hoshi, T. Suzuki, M. Ando, J. Chem. Soc., *Perkin Trans. 1*, 457 (1999).

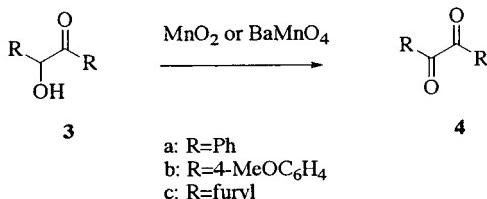
Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: allylic alcohol, manganese dioxide, barium manganate, aldehyde, ketone



- | | |
|-----------------|-----------------------------------|
| a: X=R=H | f: X=3,4-OCH ₂ O-; R=H |
| b: X=4-MeO; R=H | g: X=H; R=Me |
| c: X=4-Me; R=H | h: X=4-Br; R=Me |
| d: X=3-Me; R=H | i: X=H; R=Et |
| e: X=3-Cl; R=H | j: X=H; R=Ph |

**Experimental procedures:**

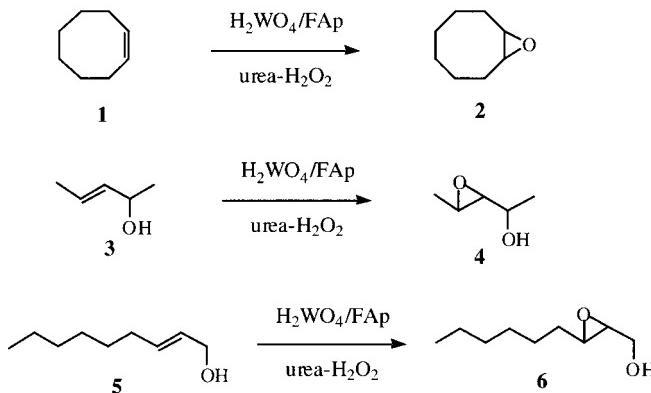
Oxidation of Benzoin to Benzil by MnO₂ as a Typical Procedure for the Oxidation of Biaryl Acyloins. A mixture of benzoin **3a** (0.212 g, 1 mmol) and MnO₂ (0.174 g, 2 mmol) was prepared and magnetically agitated in an oil bath at 90 °C for 4 h. The progress of the reaction was monitored by TLC. The reaction mixture was applied on a silica gel pad (3 g) and washed with Et₂O (20 mL) to afford pure benzil **4a** quantitatively (mp 94 °C). The same reaction with BaMnO₄ proceeded to completion after 2 h using 1.5 mmol of the oxidant.

References: H. Firouzabani, B. Karimi, M. Abbassi, *J. Chem. Res. (S)*, 236 (1999).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: olefin, allylic alcohol, epoxidation, tungstic acid, fluoroapatite, urea-H₂O₂, epoxide



Experimental procedures:

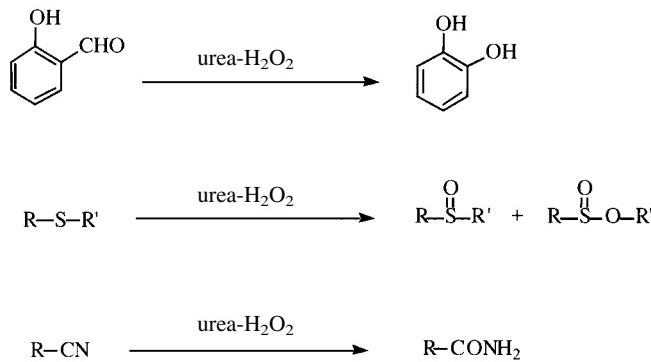
To a solid mixture of FAp powder (0.50 g) with urea-H₂O₂ powder (0.235 g, 2.5 mmol) was added tungstic acid powder (0.025 g, 0.10 mmol) in a test tube with a screw-cap, and mixed sufficiently. The solid mixture was permeated by a cyclooctene liquid **1** (0.110 g, 1.0 mmol), and the mixture was left without stirring at room temperature. After 48 h the reaction smoothly proceeded to afford epoxycyclooctane **2** in 90% yield.

References: J. Ichihara, *Tetrahedron Lett.*, **42**, 695 (2001).

Type of reaction: oxidation

Reaction condition: solid-state

Keywords: 2-hydroxybenzaldehyde, sulfide, nitrile, pyridine, urea-hydrogen peroxide complex, catechol, sulfoxide, sulfenic ester, amide, pyridine-*N*-oxide



Experimental procedures:

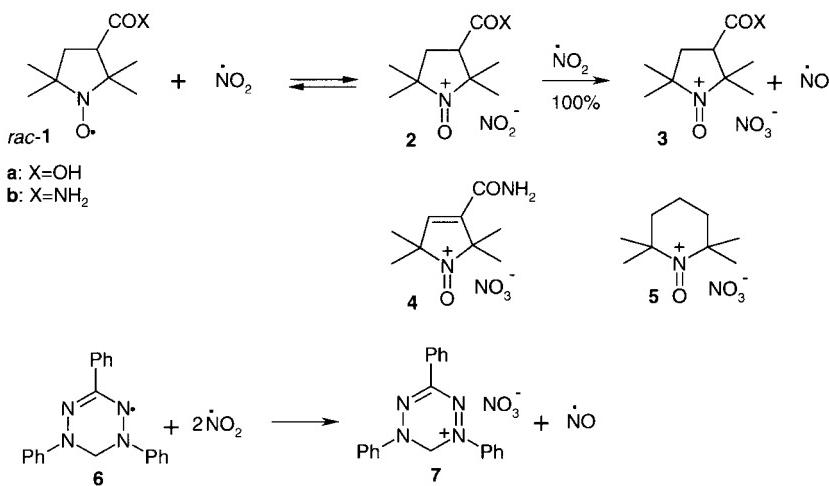
The starting material (2 mmol) was added to the finely powdered urea-hydrogen peroxide adduct (376 mg, 4 mmol) in a glass test tube, and the reaction mixture was placed in an oil bath at 85 °C. After completion of the reaction, monitored by TLC, the reaction mixture was extracted into ethyl acetate and the combined extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford the crude product, which was purified by chromatography to deliver pure product, as confirmed by the spectral analysis.

References: R. S. Varma, K. P. Naicker, *Org. Lett.*, **1**, 189 (1999).

Type of reaction: oxidation

Reaction condition: solid-state

Keywords: nitroxyl, verdazyl, nitrogen dioxide, bromine, xenon difluoride, gas-solid reaction

**Experimental procedures:**

An evacuated 100-mL flask was filled with N₂O₄/NO₂ to a pressure of 650 mbar (296 mg, 6.4 mmol NO₂). The sampling flask was connected to an evacuated 1-L flask which was then connected to an evacuated 10-mL flask that was cooled to 5 °C and contained the nitroxyl **1a**, or **1b**, or the nitroxyl precursor to **4** (500 mg, 2.70 mmol). After 1 h, the cooling bath was removed and excess NO₂ and NO were condensed to a cold trap at -196 °C for further use. The yield was 665 mg (100%) of pure **3a**, or **3b**, or **4**. (Ref. 1)

Similarly, 2 g quantities of tetramethylpiperidine-*N*-oxyl (TEMPO) were reacted at -10°C (initial pressure of NO₂ 0.03 bar) in 12 h with a quantitative yield of pure **5**. (Ref. 1)

Similarly, triphenylverdazyl **6** (200 mg, 0.64 mmol) was oxidized with NO₂ (3.2 mmol) at an initial pressure of 0.2 bar at 0°C with a quantitative yield of pure **7**. (Ref. 1)

Similarly, the corresponding bromides of **3**, **4**, **5**, **7** were quantitatively obtained if the free radical precursors were oxidized with bromine vapor in evacuated flasks. (Ref. 2)

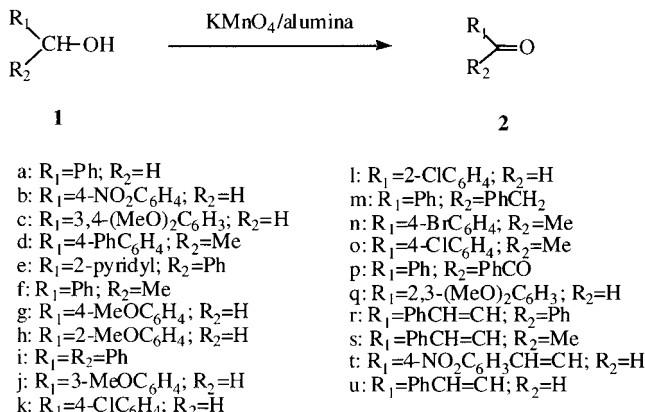
Similarly, the corresponding fluorides of **3**, **4**, **5**, **7** were quantitatively obtained by oxidation with gaseous XeF₂. (Ref. 3)

- References:**
- (1) G. Kaupp, J. Schmeyers, *J. Org. Chem.*, **60**, 5494 (1995).
 - (2) S. Nakatsuji, A. Takai, M. Mizumoto, H. Anzai, K. Nishikawa, Y. Morimoto, N. Yasuoka, J. Boy, G. Kaupp, *Mol. Cryst. Liq. Cryst.*, **334**, 177 (1999).
 - (3) G. Kaupp, *Comprehensive Supramolecular Chemistry*, Vol. 8, 381 (Ed. J.E.D. Davies), Elsevier, Oxford (1996).
-

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: alcohol, alumina-supported permanganate, ketone, aldehyde



Experimental procedures:

The alumina supported permanganate is prepared by combining KMnO₄ (4 g, 25.3 mmol) and alumina (neutral, 5 g) in a mortar and grinding with a pestle until a fine, homogeneous, purple powder is obtained. Benzoin (0.42 g, 2 mmol) is added to KMnO₄/Al₂O₃ (1 g, 2.8 mmol), the mixture was grinded with a pestle in a mortar until TLC showed complete disappearance of starting material, which

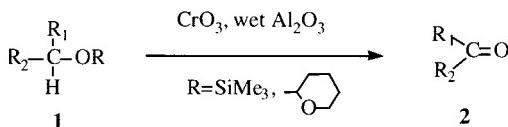
required 5 min (Table 1). Acetone (15 mL) was added to the reaction mixture and after evaporated by rotary evaporator. The residue is taken up into ether and washed with H₂O (10 mL), dried (MgSO₄) and the ether evaporated to give crude material.

References: A.R. Hajipour, S.E. Mallakpour, G. Imanzadeh, *Chem. Lett.*, 99 (1999).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: silyl ether, tetrahydropyranyl ether, deprotection, wet alumina, chromium oxide, ketone, aldehyde



a: R₁=Ph; R₂=H

e: R₁=R₂=Ph

b: R₁=4-MeC₆H₄; R₂=H

f: R₁,R₂=C₅H₁₀

c: R₁=2-NO₂-5-MeC₆H₃; R₂=H

g: R₁=PhCH=CH; R₂=H

d: R₁=Ph; R₂=Me

Experimental procedures:

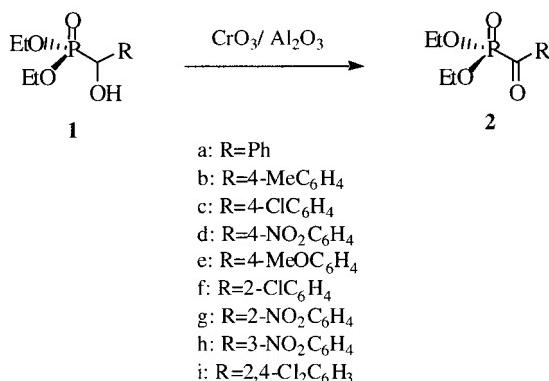
In a watch glass, neat trimethylsilyl ether **1** (1 mmol), or tetrahydropyranyl ether **2** (mmol), was mixed with the above catalyst (1 mmol) with a spatula. An exothermic reaction started with darkening of the orange color of the reagent and completion was confirmed by TLC (hexane-EtOAc, 8:2). The product was extracted into CH₂Cl₂ (2×20 mL) and is passed through a small bed of alumina (1 cm) to afford the corresponding carbonyl compound.

References: M.M. Heravi, D. Ajami, M. Ghassemzadeh, *Synthesis*, 393 (1999).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: 1-hydroxyphosphonate, Arbuzov reaction, acylphosphonate

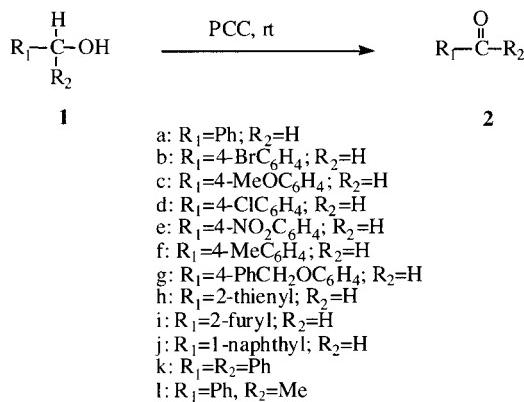
**Experimental procedures:**

Thirty mmol of the reagent is prepared by the combination of CrO₃ (30 mmol, 3 g, finely ground) and alumina (Al₂O₃, neutral, 5.75 g) in a mortar and by grinding them together with a pestle until a fine, homogeneous, orange powder is obtained (5–10 min). The 1-hydroxyphosphonate (10 mmol) is added to this reagent. After 2.5–12 h of vigorous stirring, the reaction mixture is washed with CH₂Cl₂ (200 mL), dried (Na₂SO₄), and the solvent evaporated to give the crude products. Pure product is obtained by distillation under reduced pressure in 65–90% yields.

References: B. Kaboudin, *Tetrahedron Lett.*, **41**, 3169 (2000); H. Firouzabadi, N. Iranpoor, S. Sobhani, A. Sardarian, *ibid.*, **42**, 4369 (2001).

Type of reaction: oxidation**Reaction condition:** solvent-free

Keywords: alcohol, pyridinium chlorochromate, microwave oven, ketone, aldehyde



Experimental procedures:

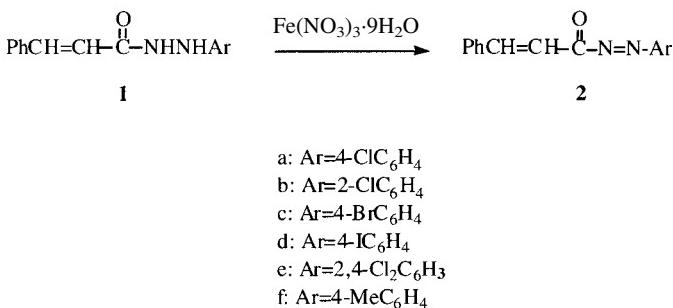
PCC (3–15 mmol) was added to the substrate (3 mmol) in a mortar. Starting materials were instantly mixed and then stored for the appropriate period at room temperature or in a microwave oven without any further agitation. The progress of the reaction was monitored by dissolving a sample in acetone and using TLC on silica gel (hexane-Et₂O, 3:1). Upon completion of the reaction, HCl (20%, 30 mL) was added and extracted with Et₂O (3 × 25 mL). The organic layer was separated and dried (MgSO₄). Evaporation of the solvent gave the corresponding carbonyl compounds in 75–96% yields.

References: P. Salehi, H. Firouzabadi, A. Farrokhi, M. Gholizadeh, *Synthesis*, 2273 (2001).

Type of reaction: oxidation

Reaction condition: solid-state

Keywords: α,β -unsaturated acyl hydrazo compound, $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$, α,β -unsaturated acyl azo compound



Experimental procedures:

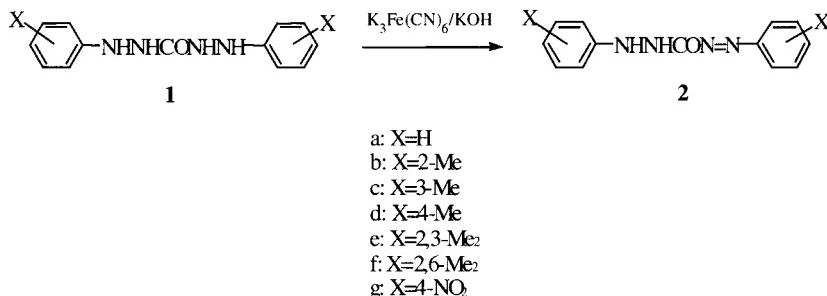
A mixture of **1** (1 mmol) and $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (2 mmol, 0.808 g) was ground in an agate mortar at room temperature until the solid mixture changed from white powder into red or brown dope with balmy odor releasing (5–10 min). The resulting mixture was extracted with acetone (10 mL). Afterwards cold water (15 mL) was added and brown, red, orange or violet-red crystals were precipitated. The products were isolated by filtrating, washed with water until the washings became neutral. The crude products were chromatographed on a column of silica (60–100 mesh) and eluted with the mixed solvent of petroleum ether ($\text{bp } 60\text{--}90^\circ\text{C}$) and acetone (5 : 1). The pure products were dried in vacuum below 50°C .

References: Y.-W. Zhao, Y.-I. Wang, H. Wang, Z.-F. Dun, X.-Z. Yao, *Synth. Commun.*, **31**, 2563 (2001).

Type of reaction: oxidation

Reaction condition: solid-state

Keywords: diaryl carbonohydrazide, $K_3Fe(CN)_6$, diaryl carbazole



Experimental procedures:

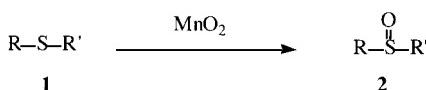
A mixture of 0.01 mol of **1** and 0.041 mol of $K_3Fe(CN)_6$ and 0.3–0.4 mmol of KOH was ground in an agate mortar. After 20–30 min, the color of the mixture turned orange-yellow, orange or dark green. Then 20 mL of water was added, then yellow, orange and orange-red and dark green products were precipitated. The product was isolated by filtration, and washed with water four times. The products were recrystallized from a mixture of ethanol and water, and dried under vacuum. Structures of these products were characterized by elemental analysis, IR and ¹H NMR spectroscopy.

References: J.-P. Xiao, Y.-L. Wang, Q.-X. Zhou, *Synth. Commun.*, **31**, 661 (2001).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: sulfide, manganese dioxide, H_2SO_4 /silica gel, sulfoxide



- a: R=Ph; R'=Me
b: R=4-Me COC₆H₄; R'=Me
c: R=Ph; R'=Et
d: R=Ph; R'=Bu
e: R=Ph; R'=i-Pr
f: R=3-Me C₆H₄; R'=i-Pr
g: R=Ph; R'=cyclopentyl
h: R=Ph; R'=cyclohexyl
i: R=R'=Pr
j: R=R'=Bu

Experimental procedures:

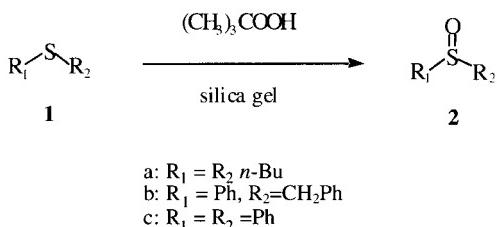
A mixture of MnO_2 (0.52 g, 6 mmol) and the catalyst (1.8 g) was added to methyl phenyl sulfide **1a** (0.37 g, 3 mmol) and the resulting solid mixture was magnetically agitated for 1 h at 35–40°C. The progress of the reaction was monitored by TLC using hexane/ Et_2O (1:1) as eluent. After completion of the reaction, the solid mixture was applied directly on a silica gel column and eluted with CHCl_3 . Evaporation of the solvent afforded almost pure methyl phenyl sulfoxide **2a** in 80% yield (0.33 g) whose physical data are consistent with those reported in the literature.

References: H. Firouzabadi, M. Abbassi, *Synth. Commun.*, **29**, 1485 (1999).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: sulfide, *tert*-butyl hydroperoxide, silica gel, sulfoxide

**Experimental procedures:**

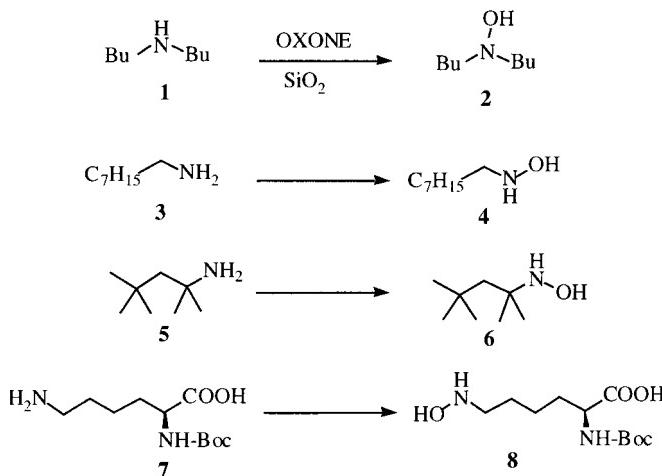
Into a 25-mL round-bottomed flask was weighed 2.5 g of Merck 10181 chromatographic silica gel that had been equilibrated with the atmosphere at 120°C for at least 48 h. The flask was stoppered and the contents allowed to cool to 25°C. The substrate was added without solvent and the resulting mixture tumbled on a rotary evaporator at atmospheric pressure until uniformly free-floating. The oxidant was then added and the mixture again tumbled. After being heated, the mixture was allowed to cool to 25°C and was washed with 100–200 mL of ethyl acetate. The adsorbent was collected by vacuum filtration and the filtrate concentrated under reduced pressure.

References: P.J. Kropp, G.W. Breton, J.D. Fields, J.C. Tung, B.R. Loomis, *J. Am. Chem. Soc.*, **122**, 4280 (2000).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: amine, surface-mediated reaction, silica gel, hydroxylamine



Experimental procedures:

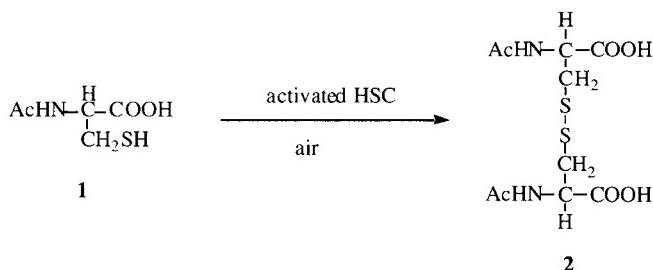
Into a 25-mL round-bottomed flask was weighed 2.5 g of Merck 10181 silica gel or Fisher A540 alumina that had been equilibrated with the atmosphere at 120°C for at least 48 h. The flask was stoppered, and the content was allowed to cool to 25°C. The amine was added without solvent and the resulting mixture tumbled until uniformly free-flowing. The oxidant was then added and the mixture again tumbled. After being heated, the mixture was allowed to cool to 25°C and was stirred overnight with 100 mL of MeOH. The adsorbent was collected by vacuum filtration and washed with an additional 50 mL of MeOH, and the combined filtrates were concentrated under reduced pressure.

References: J.D. Fields, P.J. Kropp, *J. Org. Chem.*, **65**, 5937 (2000).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: thiol, ferriprotoporphyrin(IX) chloride, peroxidase, oxidative coupling, disulfide

**Experimental procedures:**

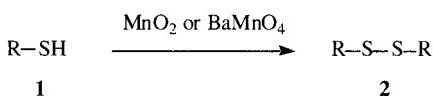
Reaction mixtures were prepared by mechanical dispersion of the thiol (200 mg g^{-1}) on the activated support. Water (0.5 mL g^{-1}) was added and the mixture was carefully mixed until an homogeneous (hydrated) loose solid was obtained. This solid was left at room temperature or heated in an open vessel for the indicated time. Products were eluted from the support either with diluted hydrochloric acid (cystine, oxidized glutathione, penicylamine) or methanol (*N*-acetylcystine, cystine methyl ester). The solution was decolorized by addition of activated carbon, filtered and evaporated.

References: E. Guibe-Jampel, M. Therisod, J. Chem. Soc., *Perkin Trans. I*, 3067 (1999).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: thiol, oxidative coupling, active manganese dioxide, barium manganese, disulfide



- a: R=Pr
- b: R=Bu
- c: R=cyclo-C₆H₁₁
- d: R=Ph
- e: R=3-MeC₆H₄
- f: R=PhCH₂

Experimental procedures:

The reaction of the thiols (3 mmol) were carried out with active manganese dioxide or barium manganate with the aid of magnetic stirrer at room temperature. 100% conversion was obtained in <5 min in each experiment. Application of the

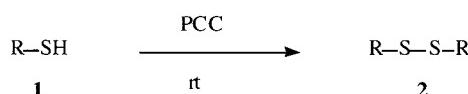
mixture on a silica gel pad followed by washing by an appropriate solvent afforded almost pure disulfide in 91–98% yields. In addition, the synthesis of diphenyldisulfide (97%) for the laboratory scale synthesis was performed successfully by using thiophenol (1.49 g, 12 mmol), active manganese dioxide or barium manganate (14 mmol) by strong magnetic agitation in about 5 min at room temperature.

References: H. Firouzabadi, M. Abbassi, B. Karimi, *Synth. Commun.*, **29**, 2527 (1999).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: thiol, pyridinium chlorochromate, oxidative coupling, disulfide



a: R=Ph	g: R=cyclohexyl
b: R=4-MeC ₆ H ₄	h: R=n-Bu
c: R=4-ClC ₆ H ₄	i: R=CH ₃ (CH ₂) ₇
d: R=3-MeC ₆ H ₄	j: R=HOCH ₂ CH ₂
e: R=2-MeOCOC ₆ H ₄	k: R=HOOCCH ₂
f: R=PhCH ₂	

Experimental procedures:

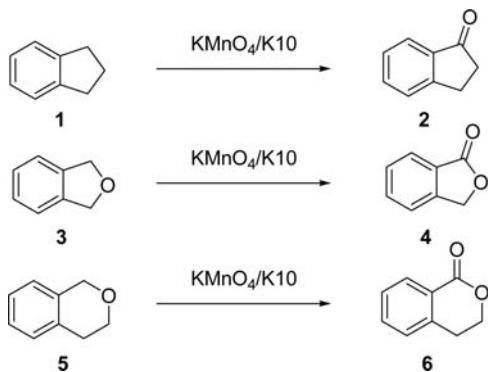
Pyridinium chlorochromate (1 mmol) was added to thiol (1 mmol) in a mortar. Starting materials were mixed and stood together for the appropriate period at room temperature. Progress of the reaction was followed by dissolving a sample in acetone and using thin layer chromatography on silica gel (MeOH-HOAc, 5:1). After completion of the reaction hydrochloric acid (20%) was added and the mixture extracted with ether (2× 20 mL) and chloroform (2× 20 mL). The organic layer was separated and dried (MgSO₄). Final evaporation of solvent gave the products in 47–94% yields.

References: P. Salehi, A. Farrokhi, M. Gholizadeh, *Synth. Commun.*, **31**, 2777 (2001).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: potassium permanganate, montmorillonite K10

**Experimental procedures:**

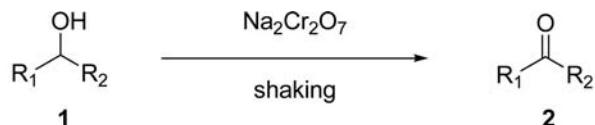
Potassium permanganate (3.16 g, 20 mmol) and montmorillonite K10 (6 g) were ground together in a mortar until a fine homogeneous powder was obtained. Indan (0.24 g, 2 mmol) was added to this $\text{KMnO}_4/\text{K10}$ mixture (4.5 g, 9.9 mmol) in a 25-mL round-bottomed flask and mixed magnetically at room temperature until TLC (eluent: hexane–ethyl acetate) analysis indicated complete reaction (20 h). The residue was then washed with CH_2Cl_2 (2×20 mL). After filtration and removal of the solvent, the crude product was chromatographed on silica gel (eluent: hexane–ethyl acetate) to give purified product (0.22 g, 1.7 mmol, 85%) which was identified by comparison with authentic 1-indanone using TLC, melting point (39–41 °C).

References: A. Shaabani, A. Bazgir, F. Teimouri, D.G. Lee, *Tetrahedron Lett.*, **43**, 5165 (2002).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: oxidation, alcohol, sodium dichromate

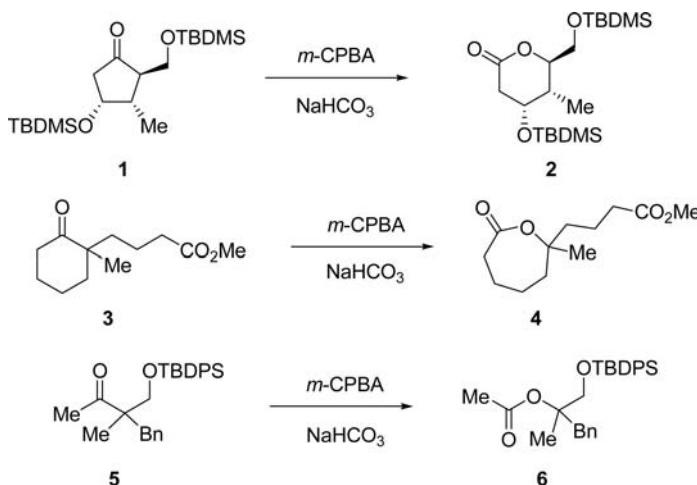


- | | |
|--|--|
| a: $\text{R}_1 = n\text{-C}_5\text{H}_{11}; \text{R}_2 = \text{H}$ | h: $\text{R}_1, \text{R}_2 = -(\text{CH}_2)_5-$ |
| b: $\text{R}_1 = \text{CH}_3\text{CCl}=\text{CH}; \text{R}_2 = \text{H}$ | i: $\text{R}_1 = \text{Ph}; \text{R}_2 = \text{Ph}$ |
| c: $\text{R}_1 = \text{Ph}; \text{R}_2 = \text{H}$ | j: $\text{R}_1 = \text{Ph}; \text{R}_2 = \text{CO}_2\text{Et}$ |
| d: $\text{R}_1 = \text{PhCH}=\text{CH}; \text{R}_2 = \text{H}$ | k: $\text{R}_1 = n\text{-C}_{15}\text{H}_{31}; \text{R}_2 = \text{CH}_2\text{CO}_2\text{Et}$ |
| e: $\text{R}_1 = p\text{-MeOC}_6\text{H}_4; \text{R}_2 = \text{H}$ | l: $\text{R}_1 = \text{Ph}; \text{R}_2 = \text{CH}_2\text{OH}$ |
| f: $\text{R}_1 = \text{CH}_2=\text{CH}; \text{R}_2 = \text{Me}$ | m: $\text{R}_1 = \text{Cyclopropyl}; \text{R}_2 = \text{H}$ |
| g: $\text{R}_1 = \text{CH}_3\text{CH}_2; \text{R}_2 = \text{Me}$ | n: $\text{R}_1 = \text{Cyclopropyl}; \text{R}_2 = \text{Cyclopropyl}$ |

Experimental procedures:

A mixture of benzyl alcohol (108 mg, 1 mmol) and $\text{Na}_2\text{Cr}_2\text{O}_7 \cdot 2\text{H}_2\text{O}$ (298 mg, 1 mmol; finely and carefully ground to around 200–300 mesh in advance) was shaken mechanically in a normal test tube (oscillation frequency: 220 times per minute; horizontal oscillator, Model: HY-2, Zhengji Instrument Co. Ltd) at room temperature for 20 min. The progress of the reaction was monitored by TLC (plates: aluminum-backed silica gel Merck 60 GF₂₅₄) using hexane–ethyl acetate (8:2) as eluent. The reaction mixture was then washed with dichloromethane (3 × 5 mL). The combined filtrates were evaporated to give crude product, which was purified by preparative TLC with hexane–ethyl acetate (8:2) to afford 103 mg (97%) benzaldehyde.

References: J. Lou, C. Gao, Y. Ma, L. Huang, L. Li, *Tetrahedron Lett.*, **47**, 311 (2006).

Type of reaction: oxidation**Reaction condition:** solvent-free**Keywords:** Baeyer–Villiger reaction, lactone**Experimental procedures:**

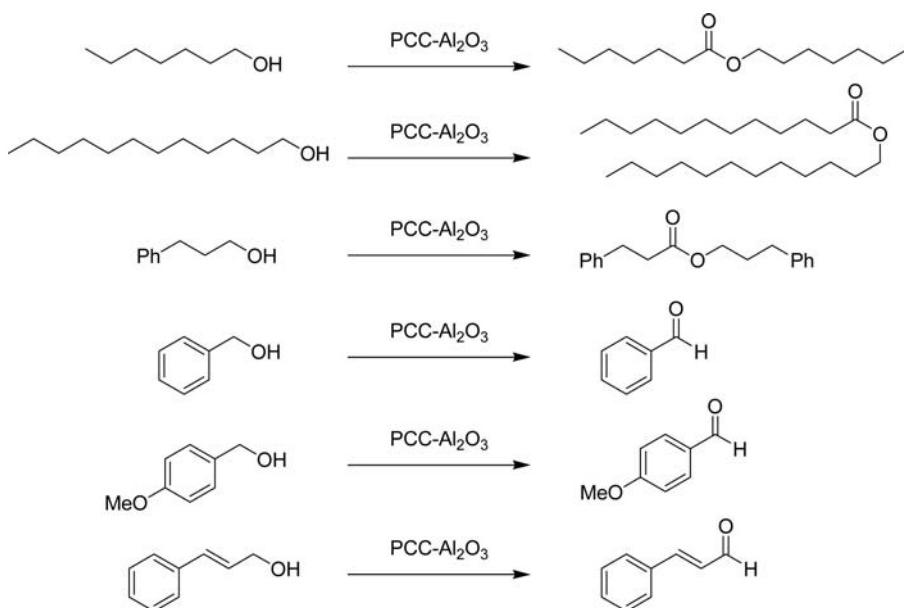
To a solution of ketone (1 mmol) and *m*-CPBA (2 mmol) in CH_2Cl_2 (3–5 mL) was added finely ground NaHCO_3 (1–2 mmol) and then the suspension was concentrated to give a solid residue. When the reaction was not completed after 3 h, a small volume of CH_2Cl_2 was added to the mixture and the whole mixture was concentrated to a solid. This process (dissolution and evaporation) was repeated every 3 h.

References: T. Yakura, T. Kitano, M. Ikeda, J. Uenishi, *Tetrahedron Lett.*, **43**, 6925 (2002).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: oxidation, pyridinium chlorochromate, alumina



Experimental procedures:

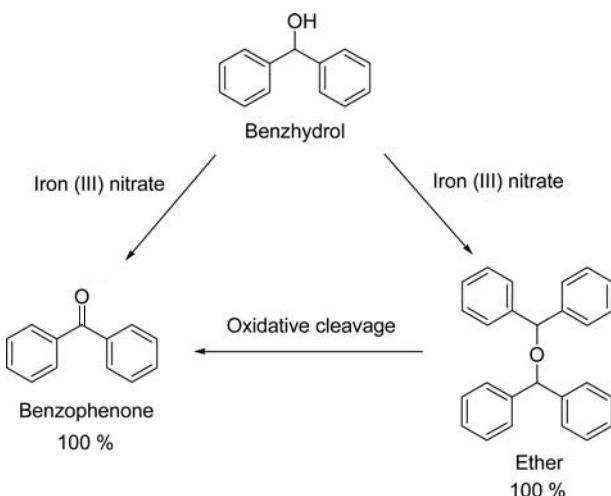
The alcohol (5 mmol) was added dropwise to the PCC-Al₂O₃ [prepared by adding activated neutral alumina (4.0 g) to a solution of PPC (1.62 g, 7.5 mmol) in dry acetone followed by evaporation of solvent to give an orange-yellow easy flowing powder] in ice-cold conditions (0–5 °C) with stirring and then kept at room temperature till the reaction was complete (as monitored by TLC). The product was isolated in almost pure form by filtration chromatography of the solid reaction mixture on a short plug of neutral alumina using diethyl ether as eluent followed by evaporation of the solvent under reduced pressure. It was further purified, if required, by column chromatography over silica gel or neutral alumina to yield the corresponding products.

References: S. Bhar, S. K. Chaudhuri, *Tetrahedron*, **59**, 3493 (2003).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: oxidation, iron (III) nitrate, benzhydrol



Experimental procedures:

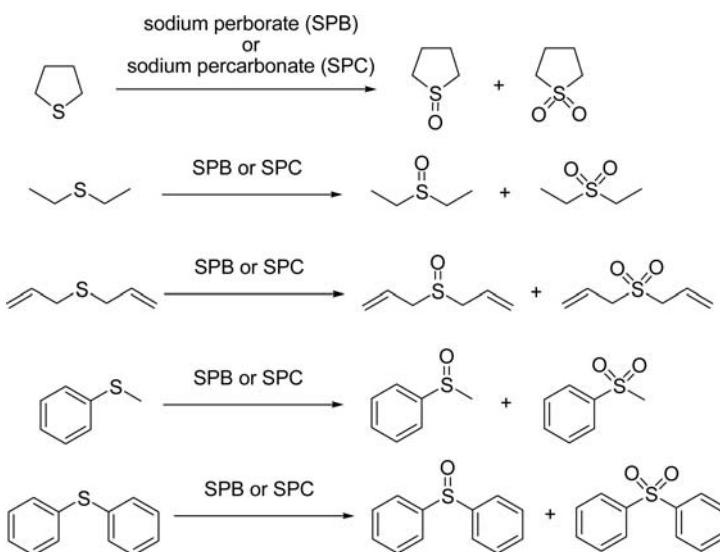
In a typical oxidation procedure, benzyl alcohol (0.324 g, 3 mmol) was admixed with $\text{Fe}(\text{NO}_3)_3 \cdot \text{H}_2\text{O}$ (0.771 g, 1.98 mmol) in a 10-mL test tube equipped with a magnetic stirrer bar and warmed at 80 °C for 15 min on a water bath. The progress of the reaction was followed by using GC-MS and TLC. Upon completion of the reaction, the mixture was cooled to room temperature and 0.5 mL water was added. The product was extracted with ether (3×3 mL) and the ether layer was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure on a rotary evaporator (0.316 g, 99%). The pure benzaldehyde was obtained by filtering through a short silica gel pad (0.310 g, 97%).

References: V.V. Namboodiri, V. Polshettiwar, R.S. Varma, *Tetrahedron Lett.*, **48**, 8839 (2007).

Type of reaction: oxidation

Reaction condition: solvent-free

Keywords: sulfide, sodium perborate, sodium percarbonate

**Experimental procedures:**

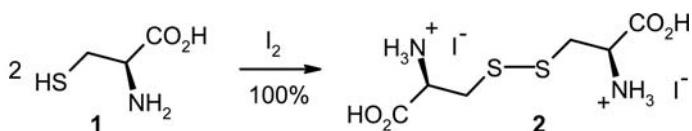
To the solid support and the finely ground oxidant (SPC or SPB as appropriate) was added the appropriate sulfide. The mixture was heated in a screw-cap sealed reaction vessel in an aluminum block at the temperature and for the time indicated. The reaction mixture was allowed to cool to room temperature. The products were isolated by extraction with methanol (60 mL). Solvent and unreacted reagent were removed *in vacuo* and the residue was weighed and analyzed by ¹H-NMR spectroscopy.

References: M. V. Gomez, R. Caballero, E. Vazquez, A. Moreno, A. de la Hoz, A. Diaz-Ortiz, *Green Chem.*, **9**, 331 (2007).

Type of reaction: oxidation

Reaction condition: solid-state

Keywords: solid-solid reaction, gas-solid reaction, cysteine, cystine, ball milling

**Experimental procedure:**

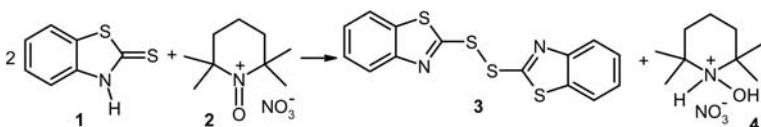
(*L*)-Cysteine **1** (242 mg, 2.00 mmol) and iodine (254 mg, 1.00 mmol) were ball-milled for 45 min at 25 °C. The colorless (*L,L*)-cystine dihydrochloride **2** (496 mg, 100%) is deliquescent in moist air.

References: G. Kaupp, *Top. Curr. Chem.* **254**, 95 (2005).

Type of reaction: oxidation

Reaction condition: solid-state

Keywords: solid-solid reaction, 2-mercaptobenzothiazole, nitrosonium salt, disulfide, ball mill



Experimental procedure:

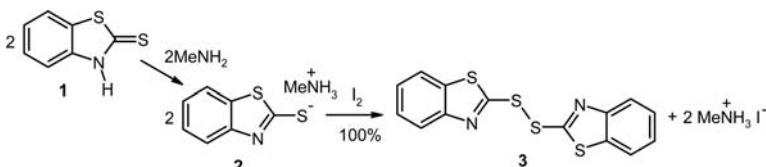
Solid 2-mercaptobenzothiazole (as benzothiazoline in the crystal) **1** (335 mg, 2.00 mmol) and the nitrosonium nitrate **2** (436 mg, 1.00 mmol) were ball-milled for 30 min to give a solid mixture of **3** and **4**. The disulfide **3** is insoluble in water, and **4** can be oxidized to the corresponding nitroxyl (TEMPO), from where **2** can be recycled by gas-solid oxidation with NO_2 .

References: G. Kaupp, *Top. Curr. Chem.* **254**, 95 (2005).

Type of reaction: oxidation

Reaction condition: solid-state

Keywords: gas-solid reaction, solid-solid reaction, 2-mercaptobenzothiazole, methylamine, iodine, disulfide, ball mill



Experimental procedure:

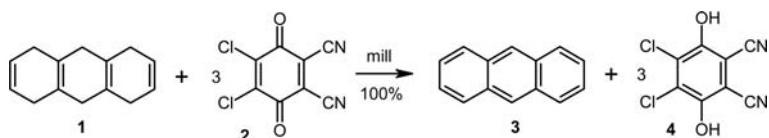
Solid 2-mercaptobenzothiazole **1** (335 mg, 2.00 mmol) was exposed to methylamine gas at 0°C (1 bar in a 100-mL flask) to form the solid active salt **2** quantitatively overnight. Excess gas was condensed to a trap at 77 K for further use. The salt **2** and iodine (254 mg, 1.00 mmol) were ball-milled for 45 min at 25°C to give the disulfide **3** (332 mg, 100%) that was isolated by washing with water and drying *in vacuo* at 80°C.

References: G. Kaupp, *Top. Curr. Chem.* **254**, 95 (2005).

Type of reaction: oxidation

Reaction condition: solid-state

Keywords: solid-solid reaction, hexahydroanthracene, anthracene, DDQ, DDQH



Experimental procedure:

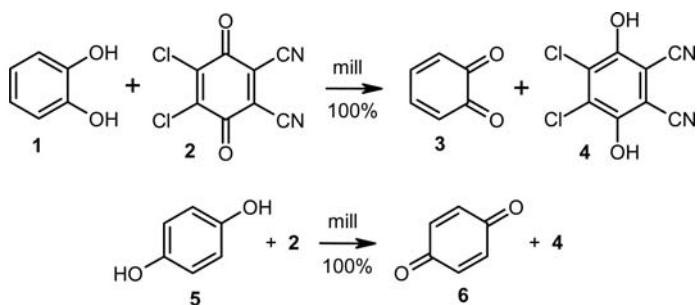
The hexahydroaromate **1** (2.00 mmol) and DDQ **2** (6.00 mmol) were ball-milled for 1 h at 25 °C to give a quantitative yield of anthracene **3**, and DDQH **4**.

References: G. Kaupp, *Top. Curr. Chem.* **254**, 95 (2005).

Type of reaction: oxidation

Reaction condition: solid-state

Keywords: solid-solid reaction, pyrocatechol, hydroquinone, *o*-benzoquinone, *p*-benzoquinone, DDQ, DDQH, Diels-Alder reagent



Experimental procedure:

Pyrocatechol **1** (2.00 mmol) and DDQ **2** (2.00 mmol) were ball-milled for 1 h at 25 °C to give a quantitative yield of *o*-benzoquinone **3** and DDQH **4**. Milling with diphenylfulvene or other dienophiles allows this mixture to be used directly for Diels-Alder reactions of labile **3**.

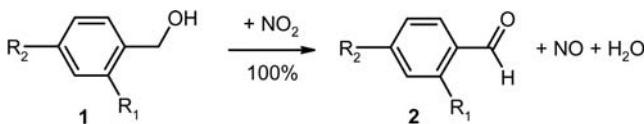
Similarly, *p*-benzoquinone **6** was obtained from hydroquinone **5** (2.00 mmol) and DDQ (2.00 mmol).

References: G. Kaupp, *Top. Curr. Chem.* **254**, 95 (2005).

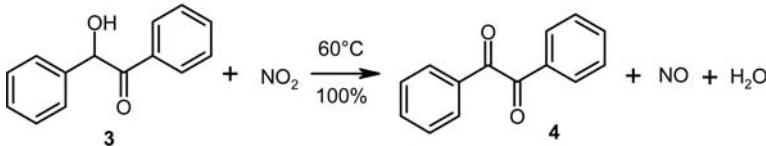
Type of reaction: oxidation

Reaction condition: solvent free

Keywords: solid-gas reaction, liquid-gas reaction, benzylic alcohols, benzaldehydes



- a: R₁ = H; R₂ = H; 5 min
- b: R₁ = H; R₂ = Me; 5 min
- c: R₁ = Cl; R₂ = H; 60 min
- d: R₁ = H; R₂ = Cl; 5 min
- e: R₁ = NO₂; R₂ = H; 60 min
- f: R₁ = H; R₂ = NO₂; 60 min



Experimental procedures:

The liquid **1a, b** or solid benzylic alcohol **1c–f** (1.00 mmol) in an evacuated 100-mL flask was exposed at 25 °C to NO₂ gas (0.6 bar, >2.7 mmol) from a lecture bottle with occasional shaking for the times given. The mixture was or became liquid. The gases of reaction were collected in a cold trap at 77 K and the water of reaction evaporated *in vacuo*, when the non-liquid benzaldehydes **2d–f** crystallized. The liquid aldehydes **2a–c** were distilled *in vacuo*. The yields of **2** were quantitative throughout [1].

The secondary alcohol *rac*-benzoin **3** (1 mmol) in a 50-mL flask at 60 °C was exposed to NO₂ gas (0.6 bar, >1.3 mmol) for 12 h to give a quantitative yield of benzil **4** after condensation of the reactant gases and drying *in vacuo* [2].

The N₂O₃ and N₂O₄ condensates in the cold trap were treated with dry air at –30 to –20 °C for complete oxidative recovery of solid N₂O₄ for further use as gaseous NO₂.

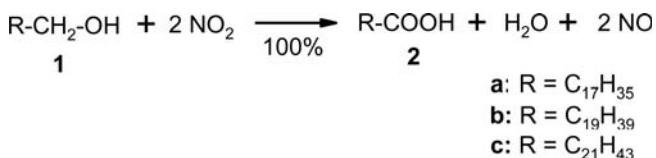
References:

1. M.R. Naimi-Jamal, H. Hamzeali, J. Mokhtari, J. Boy, G. Kaupp, *ChemSusChem* (2008), submitted; including further examples.
2. G. Kaupp, *Top. Curr. Chem.* **254**, 95 (2005).

Type of reaction: oxidation

Reaction condition: solid state

Keywords: solid-gas reaction, fatty alcohols, carboxylic acids

**Experimental procedures:**

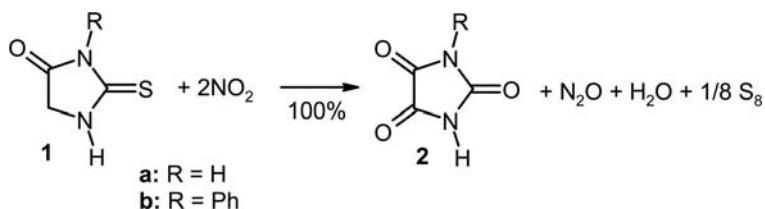
The crystalline alcohol **1** (1.00 mmol) in an evacuated 250-mL flask was exposed to NO₂ gas (0.6 bar, >7 mmol) and left at room temperature overnight. No intermediate signs of melting were observed, but the product crystals were covered with some of the water of reaction. After condensation of the gases of reaction to a cold trap at 77 K, and after thorough drying *in vacuo* a quantitative yield of the carboxylic acid **2** was obtained. The N₂O₃ and N₂O₄ condensates in the cold trap were treated with dry air at -30 to -20°C for a complete oxidative recovery of solid N₂O₄ for further use as gaseous NO₂.

References: M. R. Naimi-Jamal, H. Hamzeali, J. Mokhtari, J. Boy, G. Kaupp, *ChemSus Chem* (2008), submitted.

Type of reaction: oxidation

Reaction condition: solid-state

Keywords: gas-solid reaction, thiohydantoin, parabanic acid, nitrogen dioxide, dinitrogen oxide

**Experimental procedures:**

Thiohydantoin **1** (500 mg, **a:** 4.31 mmol, **b:** 2.63 mmol) in a 100-mL flask was exposed to NO₂ gas (0.7 bar, >16 mmol) from a 500-mL flask at a vacuum line for 6 h at room temperature. After collection of the N₂O and excess NO₂ in a trap at 77 K the sulfur was sublimed off at 100°C and 5 × 10⁻⁴ Torr. The parabanic acid **2a** (mp 245°C), or **2b** (mp 214°C) was obtained quantitatively in pure form. The gas mixture was separated by low temperature distillation for further use.

References: G. Kaupp, J. Schmeyers, *J. Org. Chem.* **60**, 5494 (1995).

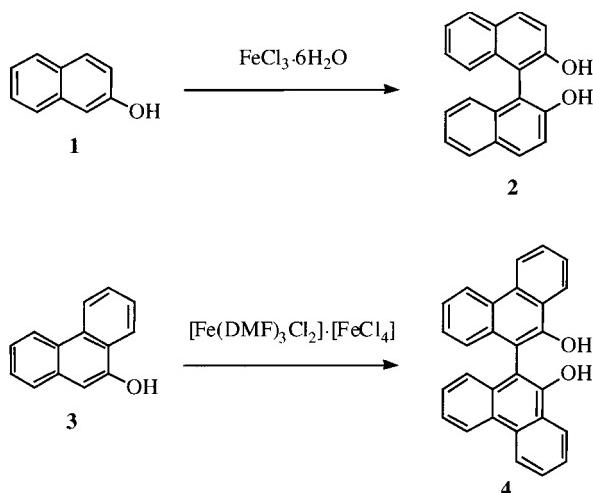
3 Carbon–Carbon Bond Formation

3.1 Solvent-Free C–C Bond Formation

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: phenol, oxidative coupling reaction, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$



Experimental procedures:

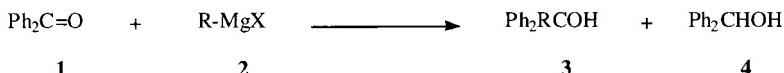
A mixture of **1** (1 g, 7 mmol) and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (3.8 g, 14 mmol) was finely powdered by agate mortar and pestle. The mixture was then put in a test tube and kept at 50°C for 2 h. Decomposition of the reaction mixture with dilute HCl gave **2** in 95% yield.

References: F. Toda, K. Tanaka, S. Iwata, *J. Org. Chem.*, **54**, 3007 (1989).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: ketone, Grignard reaction, alcohol



- a: R=Me; X=I
- b: R=Et; X=Br
- c: R=*i*-Pr; X=Br
- d: R=Ph; X=Br

Experimental procedures:

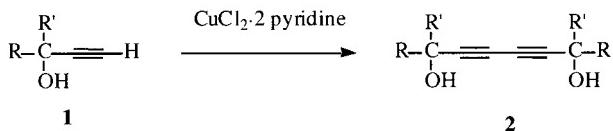
One mole of ketone and three moles of the dried Grignard reagent were finely powdered and well mixed with agate mortar and pestle, and the mixture was kept at room temperature for 0.5 h. The reaction mixture was decomposed with aqueous NH₄Cl, extracted with ether, and the extract dried over Na₂SO₄. Evaporation of the solvent gave products.

References: F. Toda, H. Takumi, H. Yamaguchi, *Chem. Exp.*, **4**, 507 (1989).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: acetylenic compound, CuCl₂, Glaser coupling, diacetylenic compound



- a: R=Ph; R'=Ph
- b: R=Ph; R'=2-ClC₆H₄
- c: R=4-MeC₆H₄; R'=4-MeC₆H₄
- d: R=Ph; R'=2,4-Me₂C₆H₃
- e: R=2,4-Me₂C₆H₃; R'=2-ClC₆H₄
- f: R=Ph; R'=Me
- g: R=Ph; R'=n-Bu
- h: R, R'=fluorenyl

Experimental procedures:

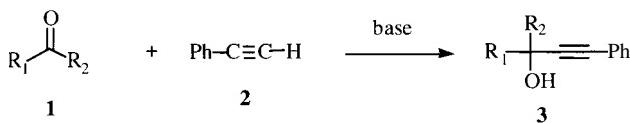
When a mixture of powdered propargyl alcohol **1a** and CuCl₂·2 pyridine complex was reacted at 50 °C for 20 h, the coupling product **2a** was obtained in 65% yield.

References: F. Toda, Y. Tokumaru, *Chem. Lett.*, 987 (1990).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: ethynylbenzene, ketone, tertiary alkynol



- a: $\text{R}_1=\text{Me}; \text{R}_2=\text{Me}$
- b: $\text{R}_1=\text{Me}; \text{R}_2=\text{Et}$
- c: $\text{R}_1=\text{Me}; \text{R}_2=n\text{-Pr}$
- d: $\text{R}_1=\text{Et}; \text{R}_2=\text{Et}$
- e: $\text{R}_1=i\text{-Pr}; \text{R}_2=i\text{-Pr}$
- f: $\text{R}_1=\text{Ph}; \text{R}_2=\text{Me}$
- g: $\text{R}_1=\text{Ph}; \text{R}_2=\text{Et}$
- h: $\text{R}_1=\text{Ph}; \text{R}_2=n\text{-Pr}$
- i: $\text{R}_1=\text{Ph}; \text{R}_2=i\text{-Pr}$
- j: $\text{R}_1, \text{R}_2=-(\text{CH}_2)_4-$
- k: $\text{R}_1, \text{R}_2=-(\text{CH}_2)_5-$
- l: $\text{R}_1, \text{R}_2=-(\text{CH}_2)_6-$

Experimental procedures:

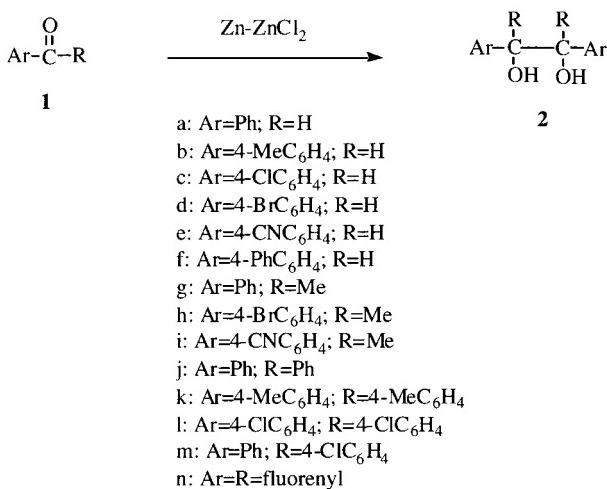
After acetone **1a** (1.0 g, 17.2 mmol), ethynylbenzene **2** (1.8 g, 17.2 mmol) and potassium *t*-butoxide (1.9 g, 17.2 mmol) were well-mixed with agate mortar and pestle, the mixture was kept at room temperature for 20 min. The reaction product was mixed with 10% aqueous sodium chloride, filtered, washed with water, and dried to give **3a** as colorless crystals (2.6 g, 94% yield).

References: H. Miyamoto, S. Yasaka, K. Tanaka, *Bull. Chem. Soc. Jpn.*, **74**, 185 (2001).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: ketone, aldehyde, pinacol coupling reaction, Zn, ZnCl_2 , *a*-glycol

**Experimental procedures:**

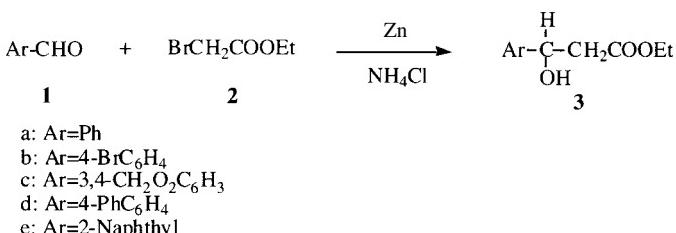
A mixture of **1** (1 g), Zn powder (5 g) and ZnCl_2 (1 g) was kept at room temperature for 3 h. The reaction mixture was combined with 3N HCl (5 mL) and toluene (10 mL) and filtered to remove Zn powder. The filtrate was extracted with toluene, and the toluene solution was washed with water and dried over MgSO_4 . The toluene solution was evaporated to give **2**.

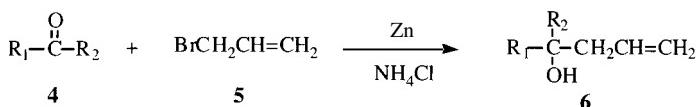
References: K. Tanaka, S. Kishigami, F. Toda, *J. Org. Chem.*, **55**, 2981 (1990).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: aldehyde, ketone, halide, Reformatsky reaction, Luche reaction, Zn, NH_4Cl , β -hydroxy ester





- a: R₁=Ph; R₂=H
- b: R₁=2-Naphthyl; R₂=H
- c: R₁=C₅H₁₁; R₂=H
- d: R₁=*trans*-CH₃CH=CH; R₂=H
- e: R₁=C₅H₁₁; R₂=CH₃
- f: R₁,R₂=-(CH₂)₅-

Experimental procedures:

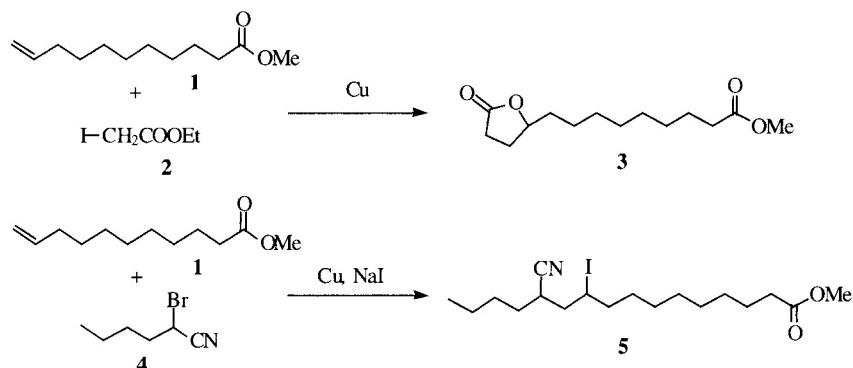
A mixture of aromatic ketone **1** (5.1 mmol), ethyl bromoacetate **2** (2.56 g, 15.3 mmol), Zn powder (5 g) and NH₄Cl (2 g) was thoroughly ground in an agate mortar and pestle, and the mixture was kept at room temperature for 23 h. The reaction product was mixed with aqueous NH₄Cl and extracted with ether. The ether solution was washed with water and dried over anhydrous MgSO₄. Evaporation of the solvent and volatile ketone in vacuo gave the product **3** in pure form.

References: K. Tanaka, S. Kishigami, F. Toda, *J. Org. Chem.*, **56**, 4333 (1991).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: alkyl 2-halocarboxylate, unsaturated carboxylic ester, radical addition, lactone



Experimental procedures:

A 50-mL, two-necked flask equipped with a magnetic stirrer, reflux condenser, and a gas inlet tube was charged with 1.3 equiv. of alkene, and 1.3 equiv. of cop-

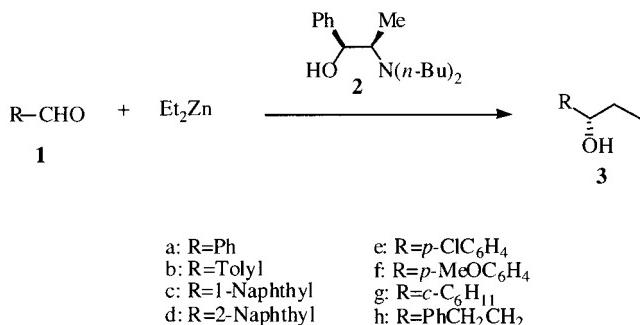
per powder (purum, Merck). The mixture was heated with constant stirring at 130 °C in an inert atmosphere. The reaction was monitored by thin-layer chromatography and was usually complete within 3–7 h. The product was isolated by distillation; alternatively, the reaction mixture was taken up into diethyl ether and after removal of copper salts by filtration and evaporation of the solvent on a rotary evaporator, the product was isolated by Kugelrohr distillation and recrystallization or flash chromatography.

References: J.O. Metzger, R. Mahler, *Angew. Chem. Int. Ed. Engl.*, **34**, 902 (1995).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: aldehyde, enantioselective addition, diethylzinc, secondary alcohol



Experimental procedures:

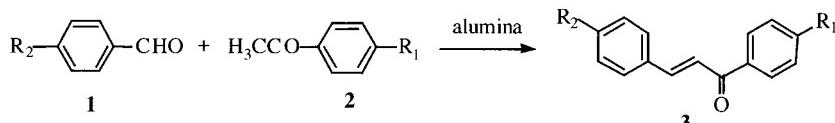
To an ice-cooled two-necked flask containing (1S,2R)-DBNE **2** (13.7 mg, 0.05 mmol), neat Et₂Zn (370 mg, 3 mmol) was transferred into the flask through a cannula under an argon atmosphere. After the mixture was stirred for 10 min at 0 °C, aldehyde **1b** (120 mg, 1.0 mmol) was added slowly to the mixture, and the mixture was stirred for 2 h. After excess Et₂Zn was removed under a reduced pressure, the reaction was quenched by saturated aq. ammonium chloride. The mixture was extracted with ether and the organic layer was dried over magnesium sulfate. Concentration and purification on silica gel TLC gave (S)-**3b** (149 mg, 99%). Ee was determined to be 90% by HPLC analysis using a chiral stationary phase (Chiralcel OB-H).

References: I. Sato, T. Saito, K. Soai, *Chem. Commun.*, 2471 (2000).

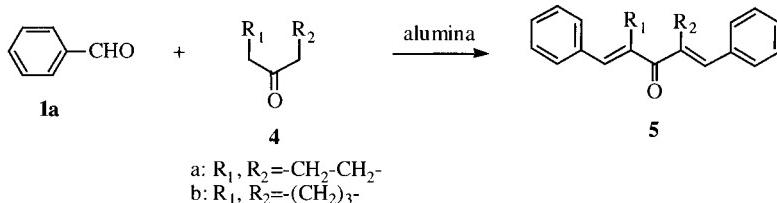
Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: benzaldehyde, acetophenone, condensation, basic alumina, chalcone



- a: $\text{R}_1=\text{R}_2=\text{H}$
- b: $\text{R}_1=\text{OCH}_3$; $\text{R}_2=\text{H}$
- c: $\text{R}_1=\text{H}$; $\text{R}_2=\text{NO}_2$
- d: $\text{R}_1=\text{H}$; $\text{R}_2=\text{COOCH}_3$



- a: $\text{R}_1, \text{R}_2=\text{CH}_2\text{-CH}_2$
- b: $\text{R}_1, \text{R}_2=(\text{CH}_2)_3$

Experimental procedures:

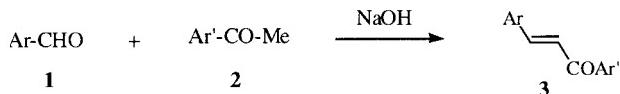
Basic alumina (13 g) was added to a mixture of methyl 4-formylbenzoate **1d** (1.00 g, 6 mmol) and acetophenone **2** (0.48 g, 4 mmol) at room temperature. (When the reactants were solid, a minimum amount (2×3 mL) of dichloromethane was used to dissolve them prior to the addition of the alumina.) The reaction mixture was then agitated at room temperature for 2.5 h using a Fisher vortex mixer. The product was extracted into dichloromethane (5×15 mL). Removal of the solvent, under reduced pressure, yielded the solid product. Further purification (removal of traces of benzyl alcohol and aldehyde) was carried out by recrystallization from a petroleum ether-ether mixture to afford 1-phenyl-3-[4-(carbomethoxy)phenyl]-2-propen-1-one **3d** (4-carbomethoxychalcone), mp 119–120 °C (81%).

References: R.S. Varma, G.W. Kabalka, L.T. Evans, R.M. Pagni, *Synth. Commun.*, **15**, 279 (1985).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: aldehyde, ketone, Aldol condensation, chalcone



- a: Ar=Ph; Ar'=Ph
- b: Ar=4-MeC₆H₄; Ar'=Ph
- c: Ar=4-MeC₆H₄; Ar'=4-MeC₆H₄
- d: Ar=4-ClC₆H₄; Ar'=Ph
- e: Ar=4-ClC₆H₄; Ar'=4-MeOC₆H₄
- f: Ar=4-ClC₆H₄; Ar'=4-BrC₆H₄
- g: Ar=3,4-Me₂C₆H₃; Ar'=4-BrC₆H₄

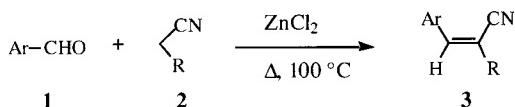
Experimental procedures:

When a slurry mixture of *p*-methylbenzaldehyde **1b** (1.5 g, 12.5 mmol), acetophenone **2b** (1.5 g, 12.5 mmol) and NaOH (0.5 g, 12.5 mmol) was ground by pestle and mortar at room temperature for 5 min, the mixture turned to a pale yellow solid. The solid was combined with water and filtered to give *p*-methyl-chalcone **3b** (2.7 g) in 97% yield.

References: F. Toda, K. Tanaka, K. Hamai, *J. Chem. Soc., Perkin Trans. 1*, 3207 (1990).

Type of reaction: C–C bond formation**Reaction condition:** solvent-free

Keywords: active methylene compound, aldehyde, Knoevenagel condensation, ZnCl₂, styrene



- a: Ar=Ph; R=CN
- b: Ar=4-MeOC₆H₄; R=CN
- c: Ar=4-ClC₆H₄; R=CN
- d: Ar=3-MeO-4-HOC₆H₃; R=CN
- e: Ar=PhCH=CH; R=CN
- f: Ar=Ph; R=CONH₂
- g: Ar=4-MeOC₆H₄; R=CONH₂
- h: Ar=4-ClC₆H₄; R=CONH₂
- i: Ar=3-MeO-4-HOC₆H₃; R=CONH₂
- j: Ar=PhCH=CH; R=CONH₂
- k: Ar=Ph; R=COOEt
- l: Ar=4-MeOC₆H₄; R=COOEt
- m: Ar=4-ClC₆H₄; R=COOEt
- n: Ar=3-MeO-4-HOC₆H₃; R=COOEt
- o: Ar=PhCH=CH; R=COOEt

Experimental procedures:

To a mixture of 0.01 mol of aldehyde **1** and 0.01 mol of active methylene compound **2**, zinc chloride (0.001 mol) was added and kept at 100 °C with constant stirring for the specified time. Then the mixture was cooled to room temperature

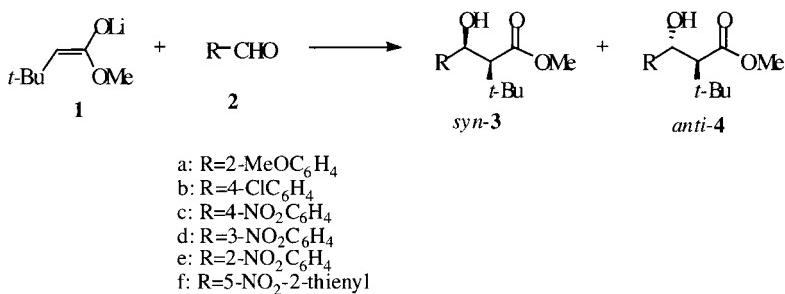
and treated with a solution of 1% aqueous alcohol to obtain the product **3** in good purity. It was filtered and dried. Recrystallization is not necessary.

References: P.S. Rao, R.V. Venkataratnam, *Tetrahedron Lett.*, **32**, 5821 (1991).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: lithium ester enolate, 3,3-dimethyl butanoate, aromatic aldehyde, Michael addition, β -hydroxy ester



Experimental procedures:

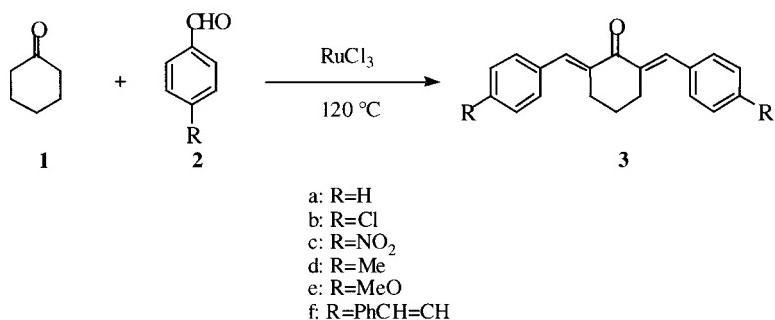
The freshly ground lithium enolate **1** (1.2 equiv.) was mixed with *o*-anisaldehyde **2a** (1 equiv.) in argon atmosphere at room temperature. The reaction was allowed to continue at room temperature under vacuum for three days, quenched with aqueous NH₄Cl and the mixture extracted with three portions of diethyl ether. The combined organic extract was washed with water and dried with anhydrous Na₂SO₄. The solvent was removed using a rotary evaporator at reduced pressure to yield the crude product. The crude product was found to contain mainly *anti* aldol product (*syn/anti* ratio 8:92). Further purification was carried out using preparative TLC with methanol-benzene (5:95 in volume) as eluent. The purified product thus isolated was a colorless solid (mp 64–65 °C, yield 70%) with the same *syn/anti* ratio as that of the crude product.

References: Y. Wei, R. Bakthavatchalam, *Tetrahedron Lett.*, **32**, 1535 (1991).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: cyclohexanone, benzaldehyde, Aldol condensation, RuCl₃, *a,a'*-bis-benzylidene cycloalkanone

**Experimental procedures:**

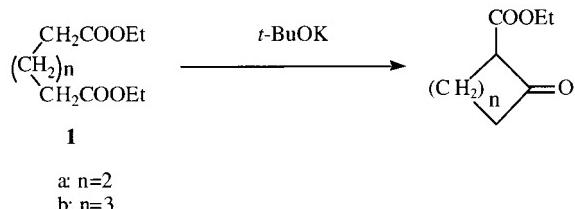
Cyclohexanone **1** (5 mmol), aldehyde **2** (10.1 mmol) and anhydrous RuCl_3 (0.1 mmol) were placed in a glass tube and sealed. The sealed tube was placed in an oil bath and heated at 120°C for 4–24 h. After cooling to room temperature, the sealed tube was opened. The reaction mixture was purified by either of the following procedures: (a) The reaction mixture was powdered, poured into cold ethanol (25 mL), stirred for 5 min and filtered. The crystalline product was further washed subsequently with water, 10% aqueous sodium bicarbonate, water, cold ethanol and dried. (b) The reaction mixture was added to 10% aqueous sodium bicarbonate (10 mL). The product was extracted with CHCl_3 (3×20 mL). The organic solution was washed with water, dried with anhydrous sodium sulfate and evaporated. Recrystallization of the product with ethanol or chromatography on a short column of silica-gel afforded the crystalline products (92–96%).

References: N. Iranpoor, F. Kazemi, *Tetrahedron*, **54**, 9475 (1998).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: diethyl adipate, diethyl pimelate, Dieckmann condensation, cyclic β -keto ester



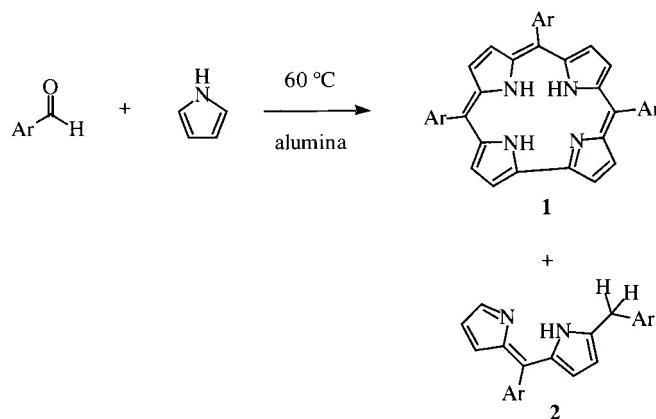
Experimental procedures:

When **1a** (10.2 g, 50.4 mmol) and *t*BuOK powder (8.44 g, 75.2 mmol) were mixed using a mortar and pestle for 10 min, the reaction mixture solidified. The solidified mixture was kept in a desiccator for 60 min. The reaction mixture was neutralized by addition of *p*-TsOH·H₂O and was distilled under 20 mmHg to give **2a** (5.8 g, 82% yield).

References: F. Toda, T. Suzuki, S. Higa, *J. Chem. Soc., Perkin Trans. I*, 3521 (1998).

Type of reaction: C–C bond formation**Reaction condition:** solvent-free

Keywords: benzaldehyde, pyrrole, alumina, corrole, oligopyrromethene

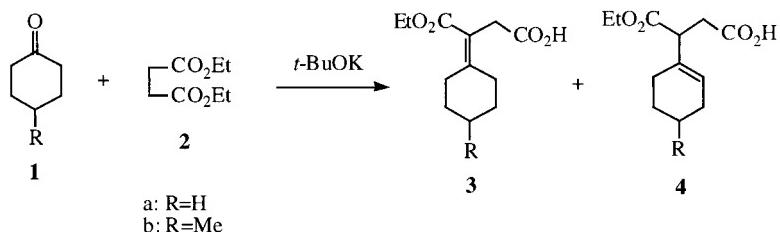
**Experimental procedures:**

The reagents (15 mmol of each) were first dissolved in CH₂Cl₂, mixed with alumina, and heated in an open vessel to 60 °C. The reaction starts only after the solvent evaporates, and a 4 h reaction time is sufficient. Column chromatographic separation gave 380 mg (12.7% yield) of the crude product **1** along with **2** (<1% yield).

References: Z. Gross, N. Galili, L. Simkhovich, I. Saltsman, M. Botoshansky, D. Blaser, R. Boese, I. Goldberg, *Org. Lett.*, **1**, 599 (1999).

Type of reaction: C–C bond formation**Reaction condition:** solvent-free

Keywords: cyclohexanone, diethyl succinate, Stobbe condensation, cyclohexylienesuccinic acid, cyclohexenylsuccinic acid

**Experimental procedures:**

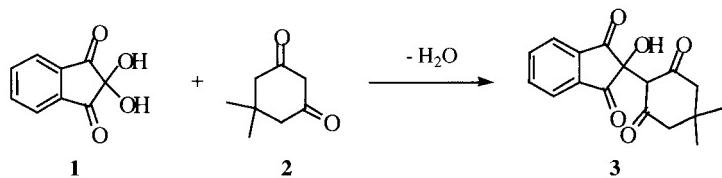
To a mixture of **1a** (1.0 g, 10.2 mmol) and **2** (1.78 g, 10.2 mmol) was added powdered *t*-BuOK (1.37 g, 12.3 mmol) in a mortar which was well ground with a pestle at room temperature for 10 min. The reaction was exposed to the air. The reaction mixture was neutralized with diluted HCl and then the crystals formed were isolated by filtration to give β -carbethoxy- β -cyclohexylidene propionic acid **3a** (colorless plates, 1.73 g) in 75% yield after recrystallization from acetone.

References: K. Tanaka, T. Sugino, F. Toda, *Green Chem.*, **2**, 303 (2000).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: ninhydrin, dimedone, ball-milling, condensation

**Experimental procedures:**

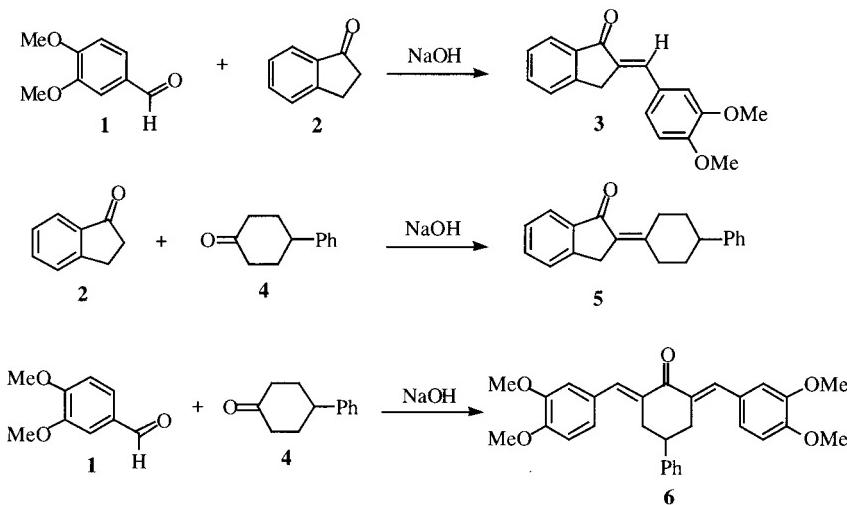
Preparation of 3: Ninhydrin **1** (178 mg, 1.00 mmol) and dimedone **2** (140 mg, 1.00 mmol) were ball-milled for 1 h at room temperature. Pure **3** (300 mg, 100%) was obtained (mp 193–195 °C, decomp.).

References: G. Kaupp, M. R. Naimi-Jamal, J. Schmeyers, *Chem. Eur. J.*, **8**, 594 (2002).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: veratraldehyde, 4-phenylcyclohexanone, 1-indanone, aldol reaction, α,β -unsaturated ketone



Experimental procedures:

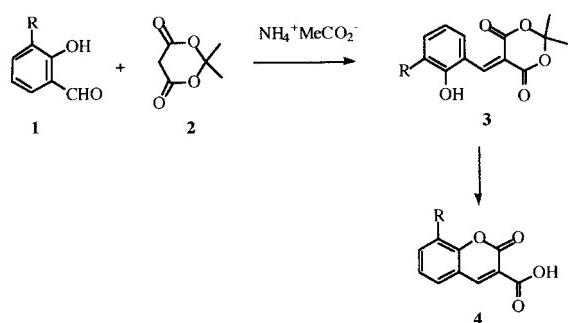
Powdered ketone and aldehyde or ketone and ketone were ground with powdered sodium hydroxide. Powdered reagents were ground intermittently, over 10 min, in a mortar and pestle or in a vibrating ball mill for a total of 2 min over a ten-minute period. In many cases reaction was observed to proceed on mixing of powdered reagents but was accelerated by grinding. The sticky solid or viscous liquids so obtained were allowed to stand (unprotected from atmospheric oxygen or water) overnight whereupon the reaction mixtures solidified. TLC of the solids after quenching with 1 M aqueous HCl indicated the presence of a single major product and the solids were worked up by quenching with dilute aqueous HCl followed by filtration of the resultant suspension. The crude product so obtained was washed with water and recrystallized from an appropriate solvent.

References: C. L. Raston, J. L. Scott, *Green Chem.*, **2**, 49 (2000).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Meldrum's acid, *o*-vanillin, Knoevenagel condensation, 3-carboxy-coumarin



Experimental procedures:

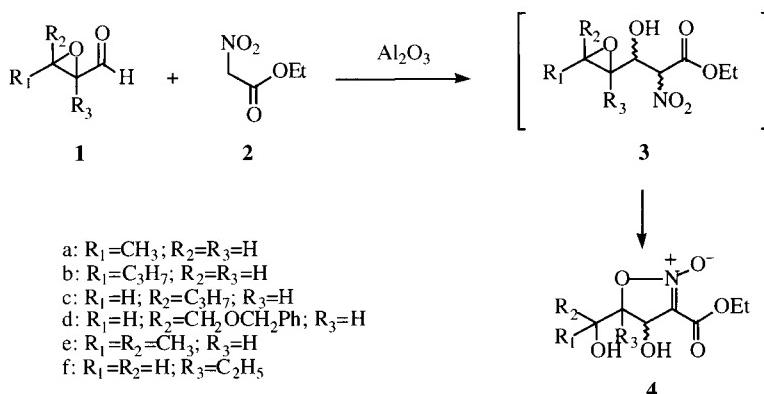
Powdered reagents (1:1 molar ratio) were gently ground together in a mortar with a pestle and a catalytic amount of $\text{NH}_4^+ \text{MeCO}_2^-$ (0.05–0.15 mol equiv. based on the benzaldehyde derivative) added and the reagents thoroughly mixed by grinding. The resulting sticky mass was allowed to stand, with occasional grinding, overnight or until no starting material was detectable by TLC analysis. The ground mixture underwent a series of color and consistency changes from white powders to sticky bright yellow material to off-white or beige solid. After regrinding, the product was suspended in water to dissolve the catalysts, filtered off, washed with water and dried on air.

References: J. L. Scott, C. L. Ratoson, *Green Chem.*, **2**, 245 (2000).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: epoxyaldehyde, ethyl nitroacetate, alumina surface, 3-(ethoxycarbonyl)-4-hydroxy-5-(1-hydroxyalkyl)-2-isoxazoline-2-oxide



Experimental procedures:

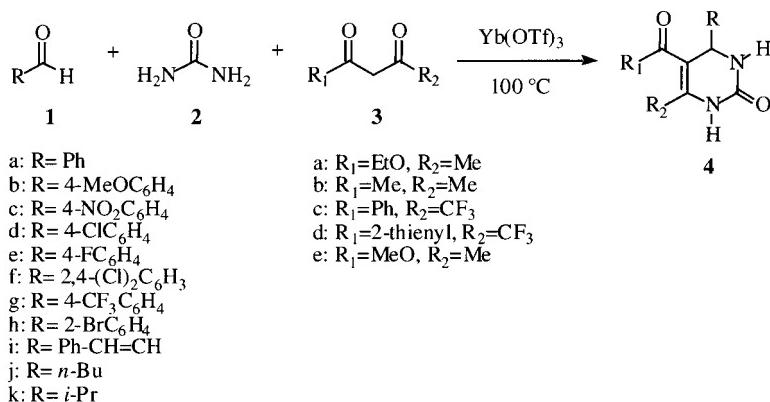
Reactions are performed simply by mixing equimolar amounts of starting materials **1** and **2** and adding to the mixture, cooled at 0 °C and under vigorous stirring, sufficient commercial chromatographic alumina to absorb it completely. After standing for 2–20 h at room temperature with occasional stirring, products are isolated in fair to good yields by washing with dichloromethane, filtration of organic extracts, and evaporation of the solvent under reduced pressure. The separation of diastereomers is accomplished by flash chromatography on silica gel using diethyl ether as eluent.

References: G. Rosini, R. Galarini, E. Marotta, P. Righi, *J. Org. Chem.*, **55**, 781 (1990).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: aldehyde, urea, β -dicarbonyl compound, Biginelli reaction, lanthanide triflate, dihydropyrimidinone



Experimental procedures:

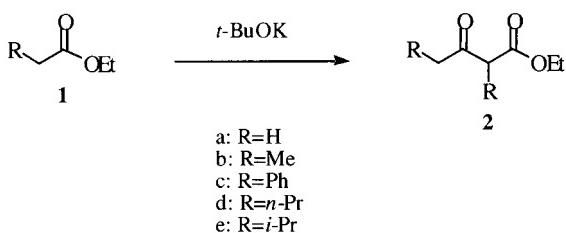
Aldehyde (2.5 mmol), β -dicarbonyl compound (2.5 mmol), urea (3.7 mmol), and Yb(OTf)₃ (0.125 mmol, 5 mol%) were heated at 100 °C under stirring for 20 min. Then water was added, and the product was extracted with ethyl acetate. After the organic layer was dried (Na₂SO₄) and evaporated, the residue was recrystallized by ethyl acetate and hexane to produce **4**. The catalyst remaining in the aqueous phase can be recovered by removing the water through heating and then drying under vacuum at 100 °C for 2 h.

References: Y. Ma, C. Qian, L. Wang, M. Yang, *J. Org. Chem.*, **65**, 3864 (2000).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: ester, Claisen reaction, Cannizzaro reaction, β -keto ester

**Experimental procedures:**

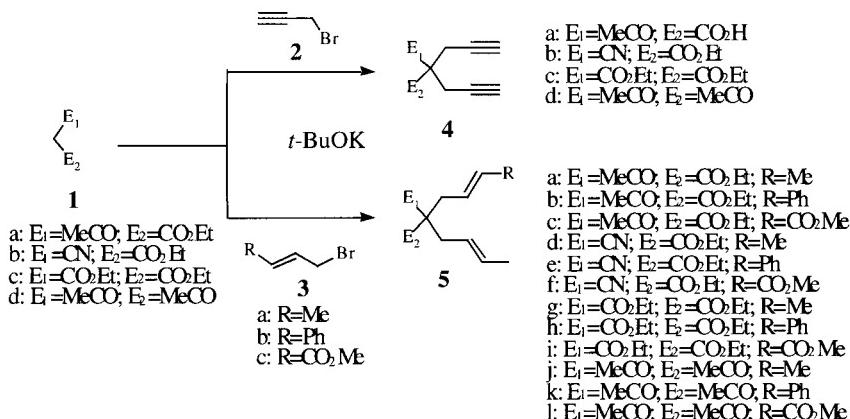
After a mixture of ethyl acetate (**1a**) (3.52 g, 40 mmol) and powdered *t*-BuOK (3.68 g, 28 mmol) was kept at 80 °C for 20 min, the reaction mixture was neutralized by addition of dil. HCl and extracted with ether. The oil left after evaporation of the solvent from the dried ether solution was distilled in vacuo by Kugelrohr apparatus to give **2a** (1.9 g, 73% yield).

References: K. Yoshizawa, S. Toyota, F. Toda, *Tetrahedron Lett.*, **42**, 7983 (2001).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: active methylene compound, unsaturated alkyl halide, alumina, potassium *tert*-butoxide, 4,4-bis-functionalized 1,6-diene, 1,6-diyne



Experimental procedures:

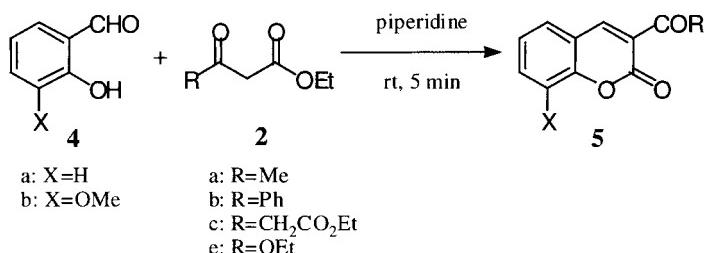
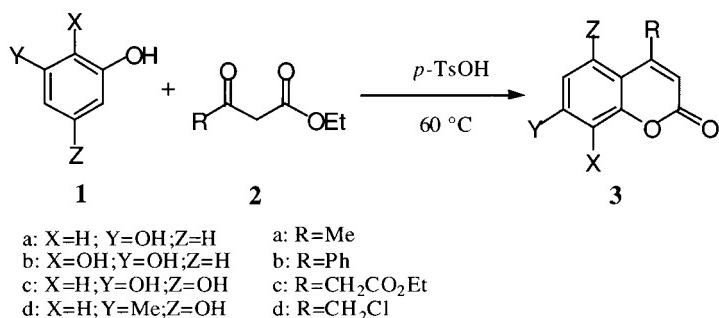
To a solution of sodium ethoxide in dry ethanol (or potassium *tert*-butoxide in dry *tert*-butanol as the case may be) (15 mmol), neutral alumina (15 times the weight of the active methylene substrate, activated by heating at 180°C under vacuum for 2 h followed by cooling and storage under argon) was added with stirring followed by evaporation of the solvent under reduced pressure to obtain an easy flowing powder. The substrate (5 mmol) was added dropwise to the supported reagent under nitrogen with vigorous stirring. Stirring was continued for 10 min at room temperature. Then the reaction mixture was cooled in ice and the alkyl halide (11 mmol) was added dropwise under stirring condition. The reaction mixture was then allowed to attain room temperature and left at room temperature with intermittent stirring (to ensure complete mixing) until completion of the reaction (monitored with TLC). The product was extracted from the solid mass by filtration chromatography over a short plug of neutral alumina using dichloromethane as solvent. Evaporation of solvent under reduced pressure furnished the crude product, which was further purified by column chromatography over neutral alumina or short path distillation.

References: S. Bhar, S.K. Chaudhuri, S.G. Sahu, C. Panja, *Tetrahedron*, **57**, 9011 (2001).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: phenol, β -keto ester, Pechmann reaction, Knoevenagel reaction, coumarin



Experimental procedures:

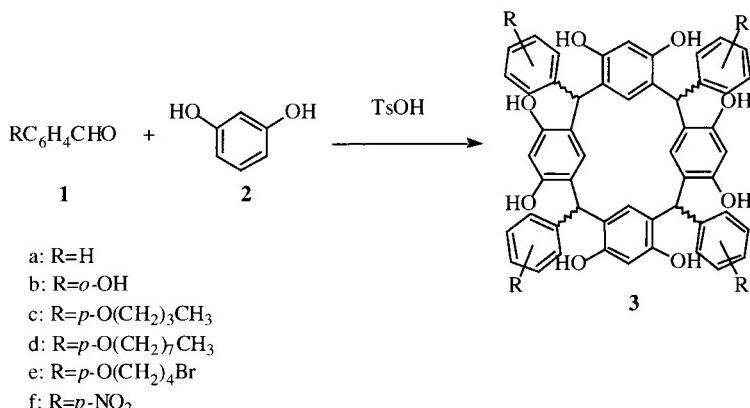
To an equivalent mixture of resorcinol **1a** (1.1 g, 10.0 mmol) and ethyl acetoacetate **2a** (1.3 g, 10.0 mmol) was added TsOH (0.3 g, 1.5 mmol) in a mortar and ground well with a pestle at room temperature. The mixture was heated at 60 °C for 10 min under atmosphere. After cooling, water was added to the reaction mixture and the crystalline products were collected by filtration to give 7-hydroxy-4-methylcoumarin **3a** (1.73 g) in 98% yield. The crude crystals thus obtained were recrystallized from EtOH to give pure **3a** as colorless prisms (mp 185–187 °C).

References: T. Sugino, K. Tanaka, *Chem. Lett.*, 110 (2001).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: benzaldehyde, resorcinol, cyclocondensation, *p*-TsOH, calix[4]resorcinarene



Experimental procedures:

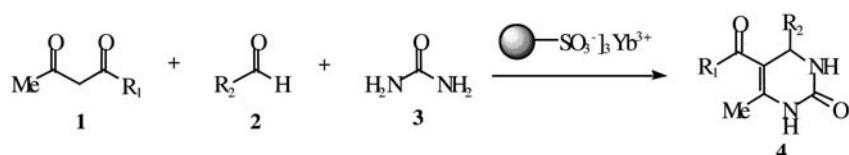
A 1 : 1 mixture of the starting aldehyde and resorcinol (0.5 to 1.0 g scale), along with a catalytic amount of *p*-toluenesulfonic acid (ca. 5%) were added together in a mortar and ground with a pestle vigorously. Within seconds a viscous paste forms which hardens on further grinding. The paste was left to stand for up to 1 h, during which time it solidified to yield a red solid. The solid was reground, washed with water to remove any acid, filtered and the pure product recrystallized with hot methanol.

References: B.A. Roberts, G.W.V. Cave, C.L. Raston, J.L. Scott, *Green Chem.*, **3**, 280 (2001).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: β -dicarbonyl compound, aldehyde, urea, Biginelli reaction, Yb(III)-resin, dihydropyrimidinone



- | | |
|--|--|
| a: R ₁ =OEt; R ₂ =C ₆ H ₅ | k: R ₁ =OEt; R ₂ =4-MeOC ₆ H ₄ |
| b: R ₁ =OMe; R ₂ =C ₆ H ₅ | l: R ₁ =OMe; R ₂ =4-MeOC ₆ H ₄ |
| c: R ₁ = <i>O</i> -Pr; R ₂ =C ₆ H ₅ | m: R ₁ = <i>O</i> -Pr; R ₂ =4-MeOC ₆ H ₄ |
| d: R ₁ =OBn; R ₂ =C ₆ H ₅ | n: R ₁ =OBn; R ₂ =4-MeOC ₆ H ₄ |
| e: R ₁ =Me; R ₂ =C ₆ H ₅ | o: R ₁ =Me; R ₂ =4-MeOC ₆ H ₄ |
| f: R ₁ =OEt; R ₂ =4-FC ₆ H ₄ | p: R ₁ =OEt; R ₂ =3-MeOC ₆ H ₄ |
| g: R ₁ =OMe; R ₂ =4-FC ₆ H ₄ | q: R ₁ =OMe; R ₂ =3-MeOC ₆ H ₄ |
| h: R ₁ = <i>O</i> -Pr; R ₂ =4-FC ₆ H ₄ | r: R ₁ = <i>O</i> -Pr; R ₂ =3-MeOC ₆ H ₄ |
| i: R ₁ =OBn; R ₂ =4-FC ₆ H ₄ | s: R ₁ =OBn; R ₂ =3-MeOC ₆ H ₄ |
| j: R ₁ =Me; R ₂ =4-FC ₆ H ₄ | t: R ₁ =Me; R ₂ =3-MeOC ₆ H ₄ |

Experimental procedures:

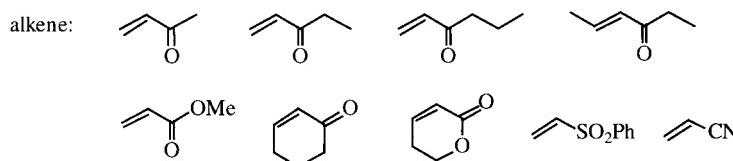
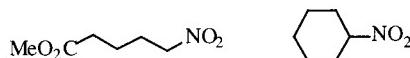
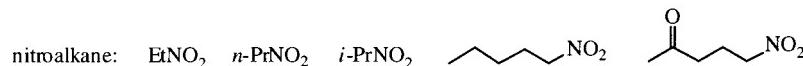
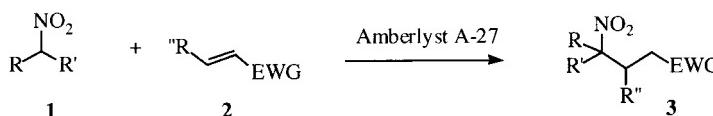
A screw-capped vial, containing a magnetic stirring bar, was charged first with 160 mg of Yb(II)-resin then with urea **3** (1.5 mmol), aldehyde **2** (0.5 mmol), and β -dicarbonyl compound (0.5 mmol) **1** and heated at 120 °C for 5 min. Then 170 mg of Yb(III)-resin were added. The reaction mixture was heated at 120 °C under gentle stirring for 48 h. After cooling to 60 °C, methanol (1 mL) was added. The suspension was stirred for an additional 30 min then the resin was filtered off and washed thoroughly with EtOAc. Amberlyst 15 (400 mg) and Ambersep 900 OH (400 mg) were added to the combined filtrates. The suspension was shaken for 2 h then the resins were filtered off and washed thoroughly with methanol. The combined filtrates were concentrated to give dihydropyrimidinones **4**.

References: A. Dondoni, A. Massi, *Tetrahedron Lett.*, **42**, 7975 (2001).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: nitroalkane, olefine, Michael addition, Amberlyst A-27, nitro compound

**Experimental procedures:**

A 100-mL two-necked flask equipped with a mechanical stirrer was charged with the nitro compound **1** (0.05 mol) and cooled with an ice-water bath. After 5 min the alkene **2** (0.05 mol) was added, and the mixture was stirred for 10 min. Am-

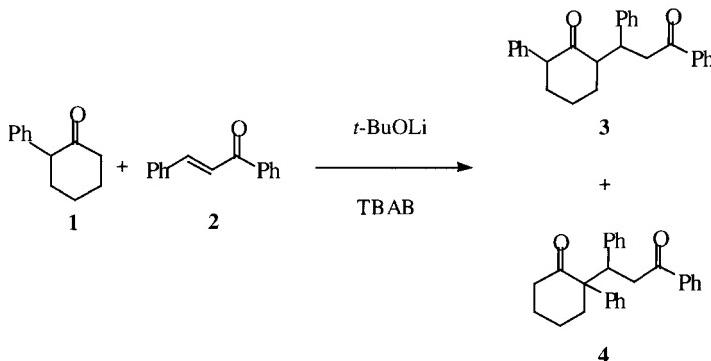
berlyst A-27 (810 g) was added, and after being stirred for 15 min, the mixture was left at room temperature for the appropriate time. The Amberlyst was washed with Et₂O (4×40 mL), the filtered extract was evaporated, and the crude nitroderivative **3** was purified by flash chromatography (cyclohexane-EtOAc).

References: R. Ballini, P. Marziali, A. Mozzicafreddo, *J. Org. Chem.*, **61**, 3209 (1996).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: 2-phenylcyclohexanone, *a,b*-unsaturated ketone, Michael addition, phase transfer catalys, 1,5-dicarbonyl compound



Experimental procedures:

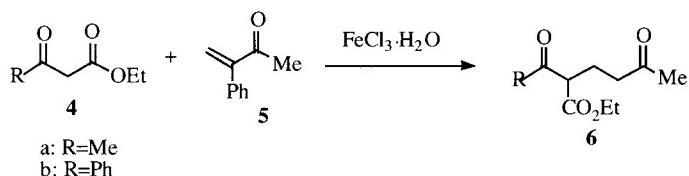
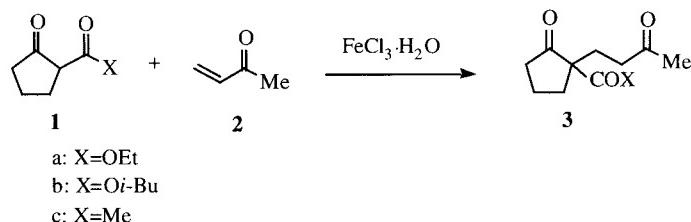
A mixture of 2-phenylcyclohexanone **1** (1.5 mmol), base (6% mol) and catalyst (6% mol) was stirred for 5 min. The Michael acceptor **2** (1.5 mmol) was then added and the reaction mixture was kept at 60 °C for 24 h. The crude mixture was extracted with dichloromethane (20 mL) and filtered. Removal of solvent and column chromatography yielded the pure products.

References: E.D. Barra, A. de la Hoz, S. Merino, P.S. Verdu, *Tetrahedron Lett.*, **38**, 2359 (1997).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: 1,3-dicarbonyl compound, *a,b*-unsaturated ketone, Michael reaction, FeCl₃·H₂O, 1,5-dicarbonyl compound



Experimental procedures:

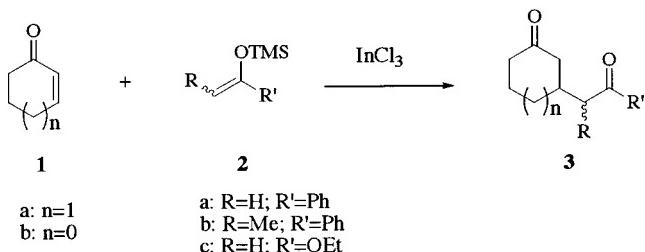
A mixture of the oxo ester **1a** (875 mg, 5.60 mmol), the enone **2** (0.500 mL, 6.00 mmol) and $\text{FeCl}_3 \cdot \text{H}_2\text{O}$ (15 mg, 0.055 mmol) was stirred overnight at room temperature, after which it was chromatographed on silica gel (hexane-MTB, 1:5; R_f 0.41) to afford **3a** as a colorless oil (1.23 g, 5.44 mmol, 97%).

References: J. Christoffers, *J. Chem. Soc., Perkin Trans. I*, 3141 (1997).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: ketene silyl enol ether, α,β -unsaturated ketone, Michael addition, indium trichloride, 1,5-dicarbonyl compound



Experimental procedures:

2-Cyclohexene-1-one **1a** (48 mg, 48.4 μL , 0.5 mmol) and indium trichloride (22.1 mg, 0.1 mmol, 20 mol%) were stirred at room temperature for 15 min and then silyl enol ether **2** (192.3 mg, 1 mmol) was added. The resulting mixture was

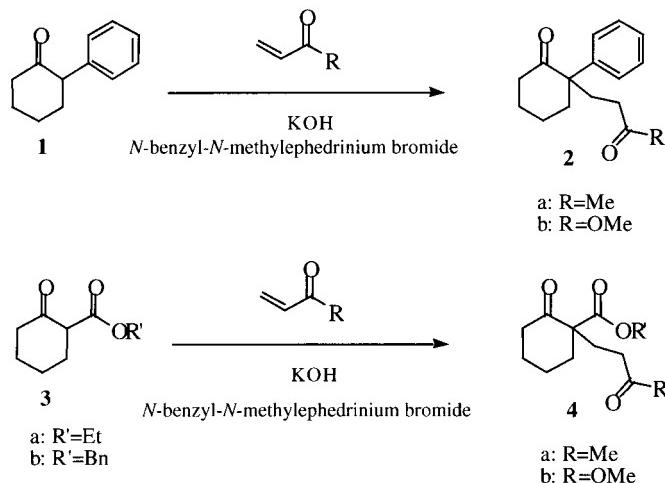
stirred at room temperature for 0.5 h and then 3 mL distilled water was added. The suspension was stirred at room temperature for 0.5 h, extracted with ethyl acetate and purified in the usual manner. The corresponding product was obtained in 67% yield (72 mg) after silica gel chromatography.

References: T. Loh, L. Wei, *Tetrahedron*, **54**, 7615 (1998).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: cyclohexanone derivative, α,β -unsaturated carbonyl compound, phase transfer reaction, Michael addition, 1,5-dicarbonyl compound



Experimental procedures:

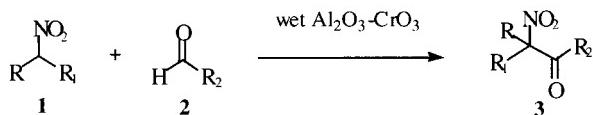
A mixture of the Michael donor (1.5 mmol) and catalytic quantities (6 mol%) of base (KOH) and the catalyst (-)-N-benzyl-N-methylephedrinium bromide was stirred for 5 min. The Michael acceptor (1.5 mmol) was then added and the mixture was stirred at 20 °C for 24 h. The crude mixture was extracted with dichloromethane (20 mL) and filtered. The solvent was removed under reduced pressure and purified by column chromatography (silica gel 230–400 mesh) to give the pure products.

References: E. Diez-Barra, A. de la Hoz, S. Merino, A. Rodriguez, P. Sanchez-Verdu, *Tetrahedron*, **54**, 1835 (1998).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: nitroalkane, aldehyde, nitroaldol reaction, alumina supported chromium(VI) oxide, *α*-nitro ketone



- a: R=Me; R₁=H; R₂=Ph(CH₂)₂
- b: R=Me; R₁=H; R₂=CH₃(CH₂)₈
- c: R=Et; R₁=H; R₂=CH₃(CH₂)₃
- d: R=Me; R₁=Me; R₂=CH₃(CH₂)₇
- e: R=Br; R₁=H; R₂=CH₃(CH₂)₈
- f: R=Me; R₁=H; R₂=c-C₆H₁₁
- g: R=Me; R₁=H; R₂=CH₃(CH₂)₉
- h: R=PhCH₂; R₁=H; R₂=Ph

- i: R=Br; R₁=H; R₂=Ph
- j: R=MeO₂C(CH₂)₃; R₁=H; R₂=CH₃(CH₂)₇
- k: R=CH₃CO(CH₂)₂; R₁=H; R₂=CH₃(CH₂)₈
- l: R=PhCH₂; R₁=Me; R₂=CH₃
- m: R=CH₃(CH₂)₃; R₁=H; R₂=Ph(CH₂)₂
- n: R=Me; R₁=H; R₂=Me
- o: R=Et; R₁=H; R₂=CH₃

Experimental procedures:

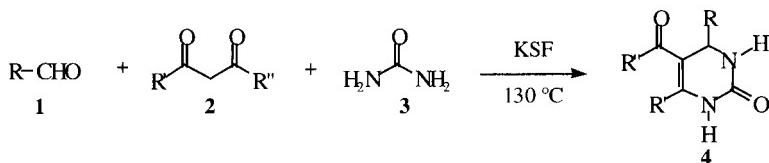
The compound **3** can be easily prepared, in one pot, through a solvent-free procedure by nitroaldol reaction of nitroalkane **1** (2.2 mmol) and aldehyde **2** (2.2 mmol, freshly distilled), on activated neutral alumina (0.6 g, the alumina was added to a mechanically stirred solution of **1** and **2**, at 0 °C, then at room temperature for 20 h). Then, in situ addition (0 °C) of wet-alumina supported chromium(VI) oxide (0.88 g (8.8 mmol) of CrO₃ and 2.64 g of wet alumina). After standing for additional 20 h, the product was extracted with diethyl ether and passed through a bed of alumina. Evaporation of the organic solvent and flash chromatographic purification afforded the pure *α*-nitro ketone **3** in good yields (68–86%).

References: R. Ballini, G. Bosica, M. Parrini, *Tetrahedron Lett.*, **39**, 7963 (1998).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: β-dicarbonyl compound, aldehyde, urea, Biginelli reaction, montmorillonite KSF, dihydropyrimidinone



- a: R=C₆H₅; R'=Me; R''=OEt
- b: R=4-ClC₆H₄; R'=Me; R''=OEt
- c: R=4-MeOC₆H₄; R'=Me; R''=OEt
- d: R=4-HOC₆H₄; R'=Me; R''=OEt
- e: R=C₆H₅CH=CH; R'=Me; R''=OEt
- f: R=C₆H₅; R'=C₆H₅; R''=OEt
- g: R=C₆H₅; R'=Me; R''=Me
- h: R=C₆H₅; R'=Me; R''=C₆H₅
- i: R=C₄H₉; R'=Me; R''=OEt

Experimental procedures:

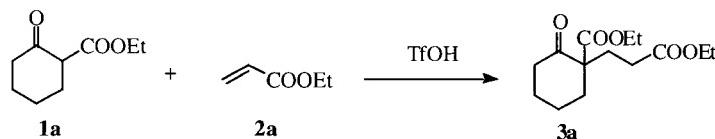
Aldehyde **1** (10 mmol), β -dicarbonyl compound **2** (10 mmol), urea **3** (0.9 g, 15 mmol) and montmorillonite KSF (0.5 g) were heated at 130 °C under stirring for 48 h. Hot methanol (100 mL) was added and the mixture was filtered to remove the catalyst. Products **4** crystallized after several hours and were recovered by filtration.

References: F. Bigi, S. Carloni, B. Frullanti, R. Maggi, G. Sartori, *Tetrahedron Lett.*, **40**, 3465 (1999).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: ethyl 2-oxo-cyclohexanecarboxylate, ethyl acrylate, Michael addition, trifluoromethanesulfonic acid



Experimental procedures:

TfOH (0.6 mmol) was added dropwise to a mixture of ethyl 2-oxocyclohexanecarboxylate **1a** (2.0 mmol) and ethyl acrylate **2a** (2.4 mmol) at 0 °C, and the resultant yellow mixture was allowed to stand at room temperature for 5 h. When the reaction was finished, the mixture turned brown. The cooled mixture was diluted with CH₂Cl₂ and neutralized by the addition of the minimum amount of

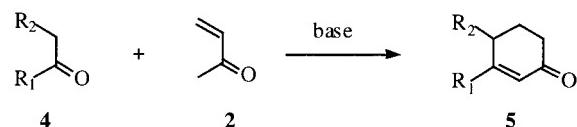
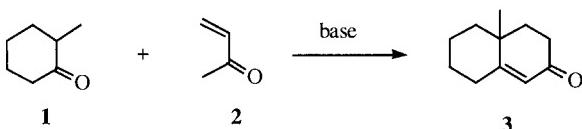
Et_3N . Concentration and purification by silica gel column chromatography gave the desired Michael adduct **3a** in 92% yield.

References: H. Kotsuki, K. Arimura, T. Ohishi, R. Maruzasa, *J. Org. Chem.*, **64**, 3770 (1999).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: α,β -unsaturated ketone, cyclohexanone, acyclic ketone, Robinson annulation reaction, decalenone, cyclohexenone



- a: $\text{R}_1=\text{Ph}; \text{R}_2=\text{H}$
- b: $\text{R}_1=\text{Ph}; \text{R}_2=\text{Me}$
- c: $\text{R}_1=\text{Ph}; \text{R}_2=\text{Et}$
- d: $\text{R}_1=\text{Ph}; \text{R}_2=\text{Ph}$
- e: $\text{R}_1=4\text{-MeC}_6\text{H}_4; \text{R}_2=\text{Ph}$
- f: $\text{R}_1=4\text{-BrC}_6\text{H}_4; \text{R}_2=\text{Ph}$
- g: $\text{R}_1=\text{Me}; \text{R}_2=\text{H}$
- h: $\text{R}_1=\text{Me}; \text{R}_2=\text{CO}_2\text{Me}$

Experimental procedures:

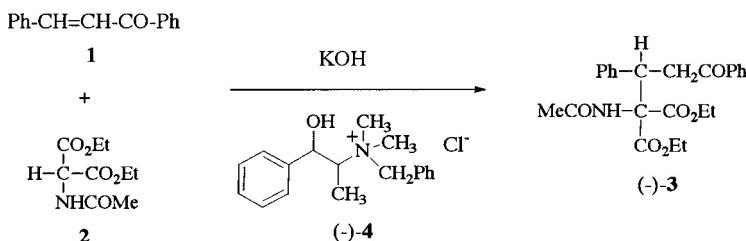
2-Methylcyclohexanone **1** (2.21 g, 20 mmol), methyl vinyl ketone **2** (4.50 g, 40 mmol), and sodium methoxide (1.2 g, 24 mmol) were well mixed with agate mortar and pestle and the mixture was kept at room temperature for 3 h. The reaction product was combined with 3M HCl (20 mL), extracted with ether (4×20 mL), and the ether solution was washed with water and dried over MgSO_4 . The dried ether solution was evaporated. Distillation of the residue in vacuo (150–170 °C/25 mmHg) gave **3** as colorless oil (1.05 g, 25% yield).

References: H. Miyamoto, S. Kanetaka, K. Tanaka, K. Yoshizawa, S. Toyota, F. Toda, *Chem. Lett.*, 888 (2000).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: chalcone, *N*-acetylaminomalonate, Michael reaction, phase transfer reaction



Experimental procedures:

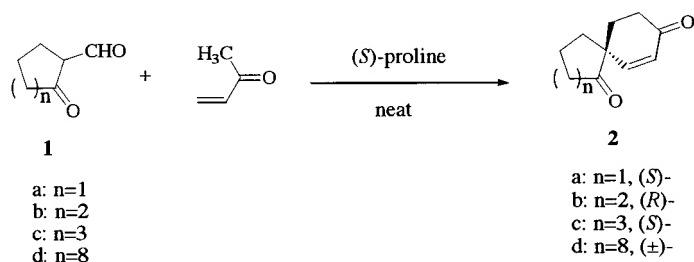
Chalcone **1** and malonate **2** in stoichiometric amounts (5 mmol) were vigorously shaken with a mechanical stirrer during 1 h at the required temperature (generally 60 °C) in the presence of catalytic quantities (6% mol) of KOH and chiral ammonium salt **4**. Then, the reaction mixture was cooled to room temperature and extracted with methylene chloride (50 mL). Product **3** was purified by chromatography on silica gel. Yield: 57%, 68% ee.

References: A. Loupy, J. Sansoulet, A. Zaparucha, C. Merienne, *Tetrahedron Lett.*, **30**, 333 (1989).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: 2-formylcycloalkanone, methyl vinyl ketone, proline, Robinson annulation, asymmetric annulation, spiro compound



Experimental procedures:

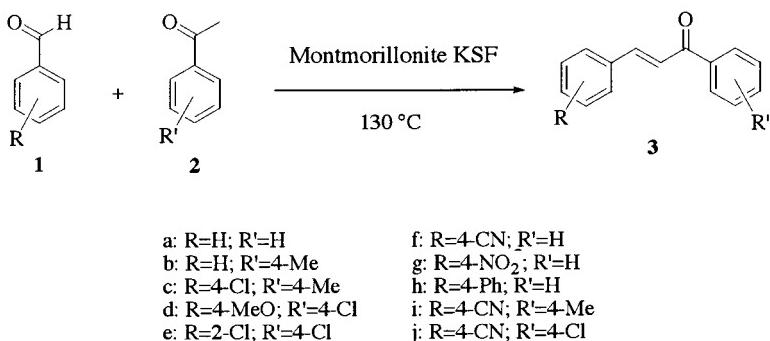
A mixture of finely ground proline (0.01 mol) and 2-formylcycloalkanone (0.01 mol) was stirred at room temperature for 2 h under a nitrogen atmosphere. Freshly distilled MVK (0.012 mol) was then added dropwise over a 30-min period. The resultant brown viscous mass was stirred with CH_2Cl_2 (150 mL) and the organic extract was washed with water (2×50 mL), brine, then dried and the solvent was removed. The residue was purified by flash column chromatography (silica gel) using chloroform as eluent.

References: D. Rajagopal, R. Narayanan, S. Swaminathan, *Tetrahedron Lett.*, **42**, 4887 (2001).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: benzaldehyde, acetophenone, montmorillonite KSF, clay, *trans*-chalcone

**Experimental procedures:**

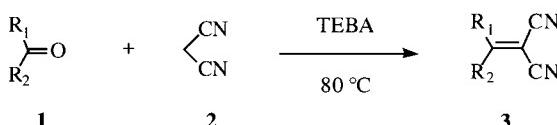
Montmorillonite KSF (1.0 g), the selected benzaldehyde **1** (0.010 mol) and the selected acetophenone **2** (0.010 mol) were placed in a small autoclave and heated at 130 °C for 18 h. After cooling to room temperature, 95% ethanol (25 mL) was added, the mixture was filtered, the catalyst washed with hot 95% ethanol (25 mL) and the products crystallized from the same solvent. All the products gave melting points and spectral data consistent with the reported data.

References: R. Ballini, G. Bosica, R. Maggi, M. Ricciutelli, P. Righi, G. Sartori, R. Sartorio, *Green Chem.*, **3**, 178 (2001).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: ketone, aldehyde, dicyanomethane, benzyltriethylammonium chloride, Knoevenagel condensation



- a: R₁=C₆H₅; R₂=H; R₃=CN
- b: R₁=C₆H₅; R₂=H; R₃=CONH₂
- c: R₁=4-NO₂C₆H₄; R₂=H; R₃=COOEt
- d: R₁=3-MeO, 4-OHC₆H₃; R₂=H; R₃=CN
- e: R₁=3-MeO, 4-OHC₆H₃; R₂=H; R₃=CONH₂
- f: R₁=furyl; R₂=H; R₃=COOEt
- g: R₁=C₆H₅CH=CH; R₂=H; R₃=CN
- h: R₁=C₆H₅CH=CH; R₂=H; R₃=COOEt
- i: R₁=i-Pr; R₂=H; R₃=CN
- j: R₁R₂=-(CH₂)₄-CH(CH₃)-; R₃=CN
- k: R₁R₂=-CH(CH₃)-(CH₂)₃-CH(CH₃)-; R₃=CN
- l: R₁=C₆H₅; R₂=CH₃; R₃=CN
- m: R₁=2-HOC₆H₄; R₂=H; R₃=COOEt

Experimental procedures:

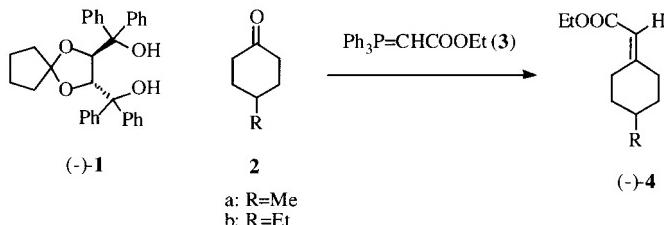
To a mixture of the carbonyl compound **1a–m** (10 mmol) and active methylene compound **2** (10 mmol) was added benzyltriethylammonium chloride (2 mmol) at room temperature. After being stirred for 5 min, the resulting mixture was heated at 80 °C in a preheated oil bath for 1 h (monitored by TLC, EtOAc-hexane, 1:9, v/v). It was then stirred and allowed to cool to room temperature when it solidified. On completion, the reaction mixture was poured into water and extracted with Et₂O (2×25 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude product thus obtained was purified by recrystallization or column chromatography to afford products **3a–m** in 40–95% yields.

References: D. S. Bose, A.V. Narsaiah, *J. Chem. Res. (S)*, 36 (2001).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: inclusion complex, stereoselective Wittig-Horner reaction, carbethoxymethylene cyclohexane



Experimental procedures:

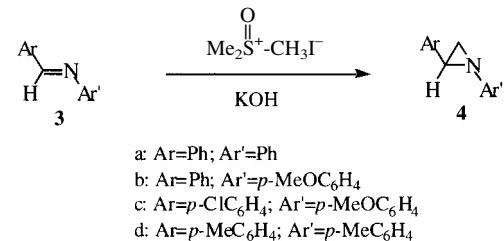
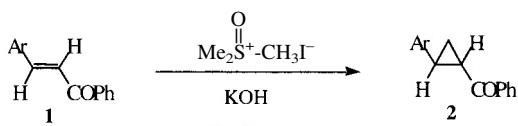
When a mixture of finely powdered 1:1 inclusion compound of $(-)\text{-1}$ and 4-methylcyclohexanone 2a (1.5 g) and (carbethoxymethyl)triphenylphosphorane 3 (2.59 g) was kept at 70°C , the Wittig-Horner reaction was completed within 4 h. To the reaction mixture was added ether-petroleum (1 : 1), and the precipitated solid (triphenylphosphine oxide and excess 3) was removed by filtration. The crude product left after evaporation of the solvent of the filtrate was distilled in *vacuo* to give $(-)\text{-4a}$ of 42.3% ee in 73% yield.

References: F. Toda, H. Akehi, *J. Org. Chem.*, **55**, 3446 (1990).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: chalcone, benzylidene aniline, trimethyloxosulfonium iodide, ylide reaction, cyclopropane, aziridine



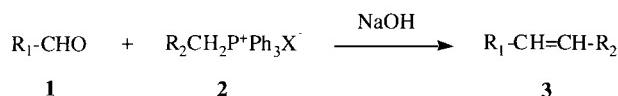
Experimental procedures:

A mixture of powdered N-benzylideneaniline **3a** (0.5 g), trimethyloxosulfonium iodide (2 g) and KOH (1.8 g) was kept at 50 °C for 3 h, after which it was washed with water. The residual crude product was taken up in diethyl ether and the ethereal solution was worked up to give aziridine **4a** as pale yellow crystals (1.2 g, 56%), mp 38–39 °C.

References: F. Toda, N. Imai, *Chem. Commun.*, 2673 (1994).

Type of reaction: C–C bond formation**Reaction condition:** solvent-free

Keywords: formylferrocene, triphenylbenzylphosphonium chloride, Wittig reaction, ferrocenylethene derivative



- a: R₁=Fc; R₂=C₆H₅; X=Cl
- b: R₁=C₆H₅; R₂=Fc; X=I
- c: R₁=Fc; R₂=p-ClC₆H₄; X=Br
- d: R₁=Fc; R₂=p-BrC₆H₄; X=Br
- e: R₁=Fc; R₂=m-NO₂C₆H₄; X=Br
- f: R₁=Fc; R₂=C₆H₅CO; X=Br
- g: R₁=Fc; R₂=p-BrC₆H₄CO; X=Br
- h: R₁=Fc; R₂=H; X=Br
- i: R₁=p-FcC₆H₄; R₂=C₆H₅; X=Cl
- j: R₁=p-MeOC₆H₄; R₂=Fc; X=I
- k: R₁=Fc; R₂=Fc; X=I

Experimental procedures:

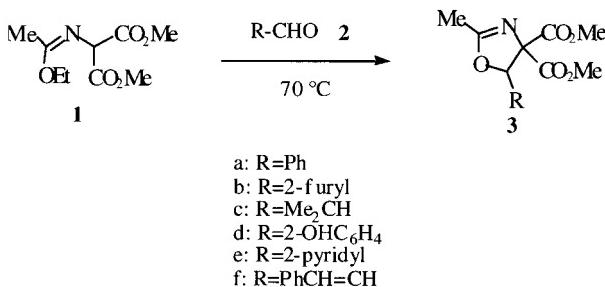
A mixture of formylferrocene **1a** (1 mmol, 0.214 g), triphenylbenzylphosphonium chloride **2a** (1.1 mmol, 0.427 g) and NaOH (1.5 mmol, 0.06 g) was thoroughly ground with a pestle in an open mortar at room temperature under atmosphere. The reaction mixture was ground for 5 min until the reaction was complete by TLC monitoring, then extracted in dichloromethane (3×20 mL). The extracts were combined and dried with anhydrous NaSO₄. After filtration, the solvent was removed under vacuum to give crude product. The residue was chromatographed on silica gel using petroleum ether as eluent. The product from the first band was a yellow oily liquid (0.055 g), which is Z-ferrocenyl-2-phenylethylene **3a**, mp 122–124 °C.

References: W. Liu, Q. Xu, Y. Ma, Y. Liang, N. Dong, D. Guan, *J. Organomet. Chem.*, **625**, 128 (2001).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: imide, dimethyl aminomalonate, aldehyde, 1,3-dipolar cycloaddition, 4,5-dihydrooxazol



Experimental procedures:

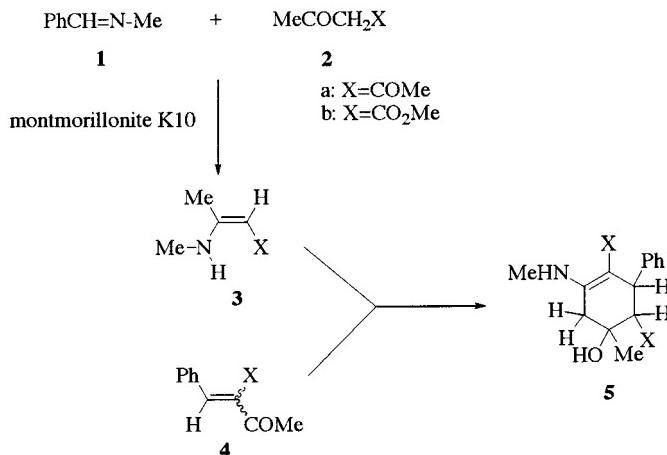
A mixture of dimethyl 2-(1-ethoxyethylidene)aminomalonate **1** (1.0 g, 4.6 mmol) and freshly distilled aldehyde **2** (4.6 mmol) was heated to 70 °C during the appropriate time (monitored by TLC) under magnetic stirring. The reaction mixture was allowed to cool down. After removal of ethanol in vacuo, the crude residue was purified by chromatography on silica gel (60F 254, Merck) with appropriate eluent. Solvent evaporation gave the desired compounds which crystallized on standing.

References: J. M. Lerestif, L. Toupet, S. Simbandhit, F. Tonnard, J. P. Bazureau, J. Hamelin, *Tetrahedron*, **53**, 6351 (1997).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: benzylidenemethylamine, acetylacetone, montmorillonite K10, enaminoketone, β -oxo alkene, cyclohexene



Experimental procedures:

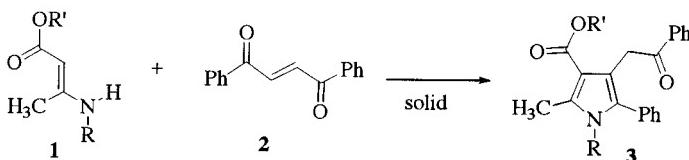
An equimolar mixture (10 mmol) of benzylidenemethylamine **1** (1.19 g) and acetylacetone **2a** (1 g) was adsorbed onto montmorillonite K10 (5 g) and allowed to stand at room temperature for 3 days. The mixture was extracted with CH₂Cl₂, the clay separated by filtration and the solvent evaporated under reduced pressure. Pure compound **3** could be isolated by short-path distillation (81% yield). The equimolar mixture of enamino ketone **3** and alkene **4a** (5 mmol) was allowed to stand at room temperature for a suitable time. Washing with suitable solvent afforded the pure solid product **5**.

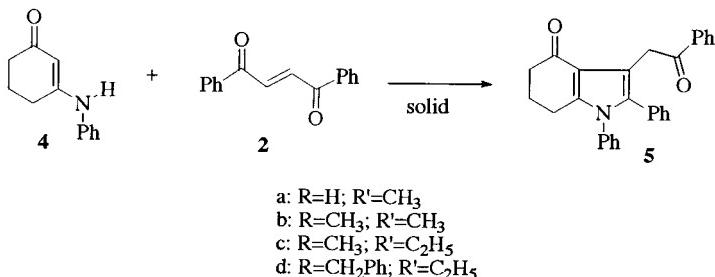
References: S.A. Ayoubi, L. Toupet, F. Texier-Boullet, J. Hamelin, *Synthesis*, 1112 (1999).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: enamine, 1,4-diphenyl-2-buten-1,4-dione, cascade reaction, solid-solid reaction, pyrroles





Experimental procedures:

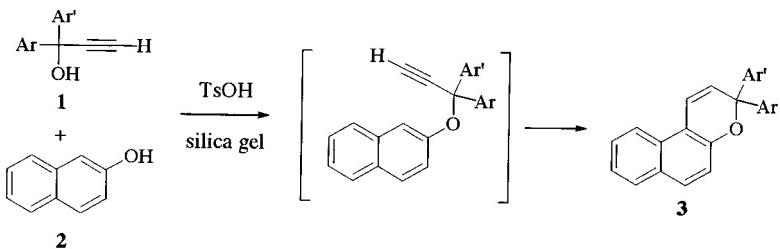
A heatable/coolable ball-mill (Retsch MM2000) with 10-mL mill beakers made from stainless steel and two stainless steel balls (6.5 g) was run at 20–30 Hz for 3 h in order to achieve quantitative conversions. Milling of **1a–d** or **4** (2.00 mmol) and **2** (2.00 mmol; mp 111 °C) gave dust-dry powders that were heated to 80 °C for removal of the water of reaction. Compound **3c** was obtained as a 2:3 mixture with its precursor and was obtained in pure form after heating to 150 °C for 5 min in order to complete the elimination and removal of water.

References: G. Kaupp, J. Schmeyers, A. Atfeh, *Angew. Chem. Int. Ed. Engl.*, **38**, 2896 (1999).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 1,1-diaryl-2-propyn-1-ol, 2-naphthol, silica gel, TsOH, naphthopyran



- a: Ar=Ph; Ar'=Ph
 b: Ar=Ph; Ar'=4-MeOC₆H₄
 c: Ar=4-MeC₆H₄; Ar'=4-MeC₆H₄
 d: Ar=Ph; Ar'=2,4-Me₂C₆H₃
 e: Ar=4-ClC₆H₄; Ar'=4-ClC₆H₄
 f: Ar, Ar'=Fluorenyl

Experimental procedures:

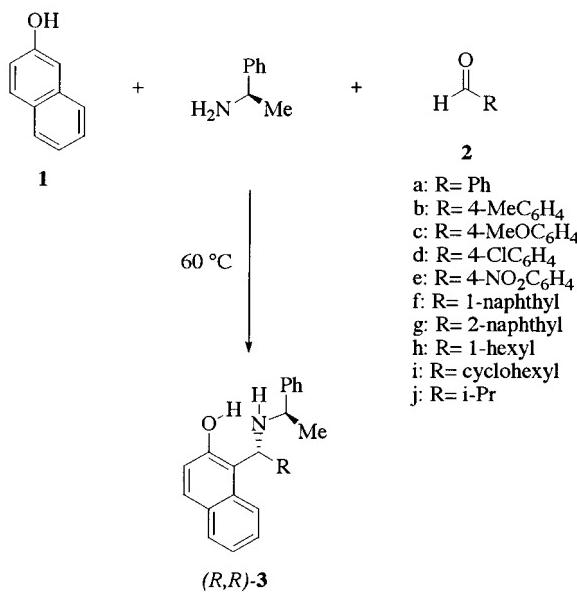
A mixture of **1a** (0.5 g, 2.4 mmol), **2** (0.34 g, 2.4 mmol), *p*-TsOH (0.046 g, 0.24 mmol), and silica gel (1.0 g) was ground for 10 min at room temperature using a mortar and pestle, and the mixture was kept for 1 h. The reaction mixture was chromatographed on silica gel using toluene as eluent to give **3a** (0.45 g, 56% yield, mp 160–162 °C) as colorless needles.

References: K. Tanaka, H. Aoki, H. Hosomi, S. Ohba, *Org. Lett.*, **2**, 2133 (2000).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: 2-naphthol, aldehyde, 1-phenylethylamine, asymmetric aminoalkylation aminoalkynaphthol

**Experimental procedures:**

A mixture of 2-naphthol **1** (0.72 g, 5.0 mmol), benzaldehyde **2a** (0.64 g, 6.00 mmol), and (*R*)-(+)1-phenylethylamine (0.64 g, 5.25 mmol) was stirred at 60 °C for 8 h under nitrogen atmosphere. Following the progress of the reaction by TLC and ¹H NMR, it was seen that the formation of the product occurs during the first 4 h but the initial dr of (*R,R*)-**3a** (2.6 at 2 h) increases over time (99 at 8 h) with the formation of a solid and crystalline reaction mixture. The reaction mixture was dispersed at room temperature with EtOH (5 mL). The white crystals separated were collected and washed with EtOH (3×3 mL). The crystal-

line white residue, purified by crystallization from EtOAc-hexane, gives the pure (*R,R*)-**3a** (1.64 g, 4.65 mmol, 93% yield).

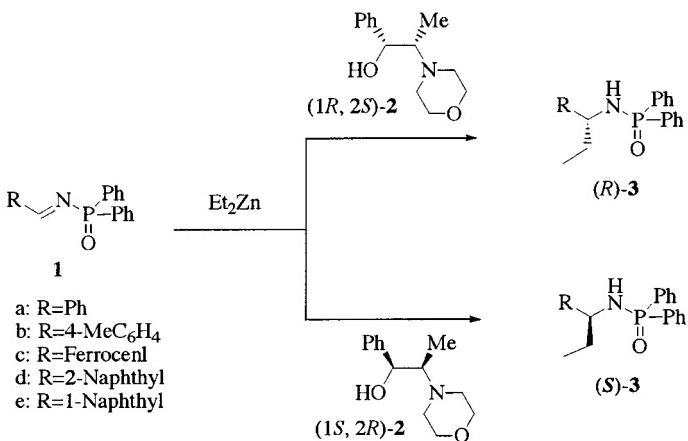
References: C. Cimarelli, A. Mazzanti, G. Palmieri, E. Volpini, *J. Org. Chem.*, **66**, 4759 (2001); C. Cimarelli, G. Palmier, E. Volpini, *Tetrahedron: Asymmetry*, **13**, 2417 (2002).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: *N*-diphenylphosphinylimine, diethylzinc, enantioselective addition, *N*-diphenylphosphinylamine

Experimental procedures:



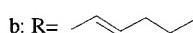
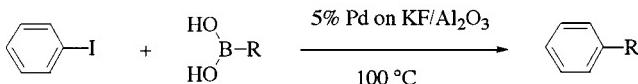
To an ice-cooled two-necked flask containing *N*-diphenylphosphinoylimine **1c** (0.21 g, 0.5 mmol) and (1*R*,2*S*)-2-morpholino-1-phenylpropan-1-ol **2** (0.11 g, 0.5 mmol), neat Et₂Zn (0.49 g, 4 mmol) was transferred through a cannula under an argon atmosphere. After the mixture was stirred at 0 °C for 2 h, the completion of the reaction was confirmed by TLC analysis. After additional stirring for 2.5 h, excess Et₂Zn was removed under reduced pressure and saturated aq. ammonium chloride was added to the residue. The mixture was extracted with dichloromethane and the combined organic layer was dried over anhydrous sodium sulfate. Concentration of the organic layer and purification of the residue on silica gel TLC gave (*R*)-**3c** (0.13 g, 58%). The ee was determined to be 97% by HPLC analysis using a chiral stationary phase (Chiralpak AS).

References: I. Sato, R. Kodaka, K. Soai, *J. Chem. Soc., Perkin Trans. 1*, 2912 (2001).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: iodobenzene, alkylboronic acid, Suzuki coupling, palladium-doped KF/Al₂O₃, alkylbenzene



Experimental procedures:

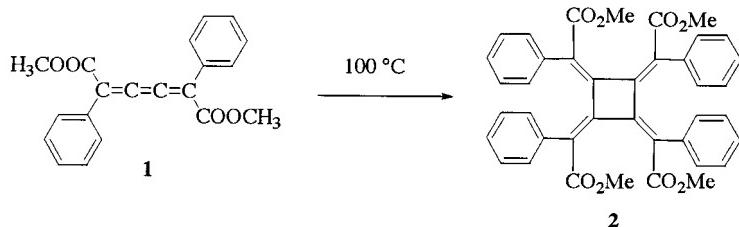
To a mixture of KF/Al₂O₃ (0.950 g, 40 wt %) and palladium black (0.050 g, 0.470 mmol, 99.9+% as a submicron powder) was added *p*-methylphenylboronic acid (0.150 g, 1.1 mmol) contained in a clean, dry, round-bottomed flask. The solid mixture was stirred at room temperature in the open air until homogeneous. Iodobenzene (0.209 g, 1.02 mmol) was then added with stirring. The mixture was stirred at room temperature for an additional 1520 min to ensure efficient mixing. A condenser was put in place and the flask placed in a preheated oil bath (100 °C). Stirring was continued during the entire reaction period. After the allotted time period, the oil bath was removed and the reaction allowed to cool to room temperature. A small quantity of hexanes was then added and the slurry stirred at room temperature for an additional 20–30 min to ensure product removal from the surface. The mixture was vacuum filtered through a sintered glass funnel using Celite as a filter aid. The mixture was separated via flash chromatography to yield 4-methylbiphenyl in 89% yield.

References: R. S. Varma, K. P. Naicker, *Org. Lett.*, **1**, 189 (1999).

Type of reaction: C–C bond formation

Reaction condition: solid state

Keywords: cumulene derivative, [2+2]cycloaddition, [4]radialene tetracarboxylic acid

**Experimental procedures:**

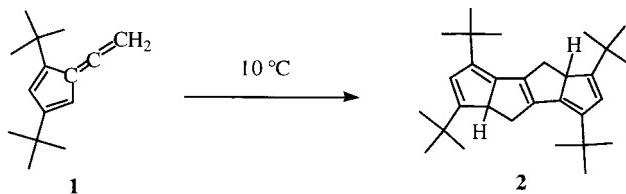
The crystals of the ester *E*-**1** underwent complete reaction within 5 days without any observable melting during conversion. Aside from a small amount of polymeric material (<5%), only a bright yellow substance was formed, which, after column chromatographic separation of the polymeric material, could be isolated in crystalline form in 75% yield.

References: F. W. Nader, C. Wacker, *Angew. Chem. Int. Ed. Engl.*, **24**, 852 (1985).

Type of reaction: C–C bond formation

Reaction condition: solid state

Keywords: 1,3-di-*tert*-butyl-5-vinylidenecyclopentadiene, [6+2]cycloaddition

**Experimental procedures:**

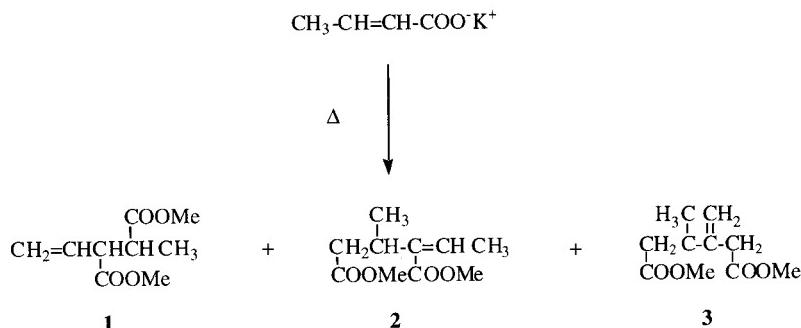
1 dimerizes in a solid-state reaction at ca. 10 °C within approx. 14 days to give 1,3,5,7-tetra-*tert*-butyl-4,4a,8,8a-tetrahydronaphthalene **2** (from *n*-hexane, pale yellow crystals, decomp. above 114 °C; yield 35%).

References: B. Stowasser, K. Hafner, *Angew. Chem. Int. Ed. Engl.*, **25**, 466 (1986).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: potassium crotonate, dimerization, hex-1-ene-3,4-dicarboxylate



Experimental procedures:

A sample (ca. 1 g) of K-crotonate was placed in a Pyrex tube (6 mm i.d. (\times 200 mm) and heated in a metal bath maintained at a constant temperature. The tube was evacuated through the reaction. After a given time the reaction tube was taken out of the bath and allowed to cool to room temperature. The heat-treated salt was weighed and dissolved in aqueous hydrochloric acid solution and extracted with ether. The ether extract was treated with diazomethane. The methyl ester derivatives of the products were subjected to analysis by gas chromatography using diethyl maleate as internal standard.

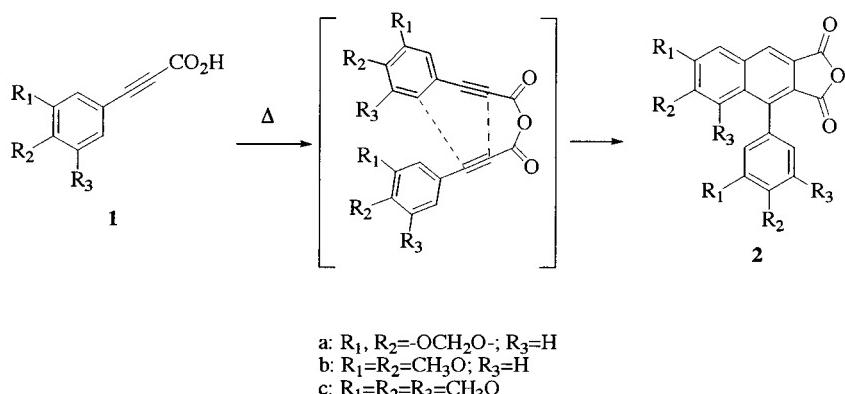
Isolation and spectral analysis of the dimer: K-crotonate (100 g) was heated at 320 °C for 4 h and subsequently treated as described above. The methyl esters (42 g), bp 100–135 °C at 6 mmHg, were fractionally distilled to give three components: dimethyl hex-1-ene-3,4-dicarboxylate **1**, bp 97 °C at 8 mmHg; dimethyl 4-methyl-pent-2-ene-3,5-dicarboxylate **2**, bp 118 °C at 5 mmHg; dimethyl 2-methylene-3-methylbutyl-1,4-dicarboxylate **3**, bp 129 °C at 8 mmHg.

References: K. Naruchi, M. Miura, *J. Chem. Soc., Perkin Trans. 2*, 113 (1987).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: (alkoxyphenyl)propionic acid, Diels-Alder reaction, anhydride



Experimental procedures:

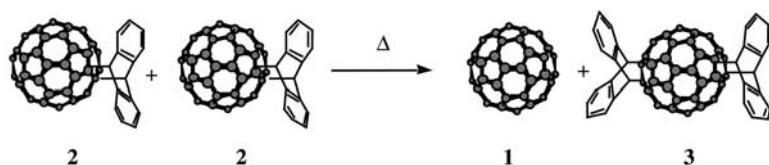
The solid-state reactions were carried out by taking approximately 100–500 mg of the powdered phenylpropionic acids **2a–c** in round-bottomed flasks. The flasks were lightly plugged with cotton and kept in oil baths at appropriate temperatures between 70–110°C. Within 27 days, the samples became discolored and some sublimed acid and phenylacetylene could be seen coated at the top of the flask. The mixtures were stirred occasionally, and after 46 weeks, the reaction mixtures were separated by column chromatography. The following reaction details were noted for acids **2a–c** (acid, percent conversion to Diels-Alder anhydride, percent unreacted plus sublimed acid, time of reaction, temperature of reaction): **2a**, 25%, 32%, 5 weeks, 95°C; **2b**, 30%, 25%, 6 weeks, 90°C; **2c**, 20%, 30%, 3 weeks, 90°C.

References: G. R. Desiraju, K. V. R. Kishan, *J. Am. Chem. Soc.*, **111**, 4838 (1989).

Type of reaction: C–C bond formation

Reaction condition: solid state

Keywords: fullerenes, topochemistry, anthracene



Experimental procedures:

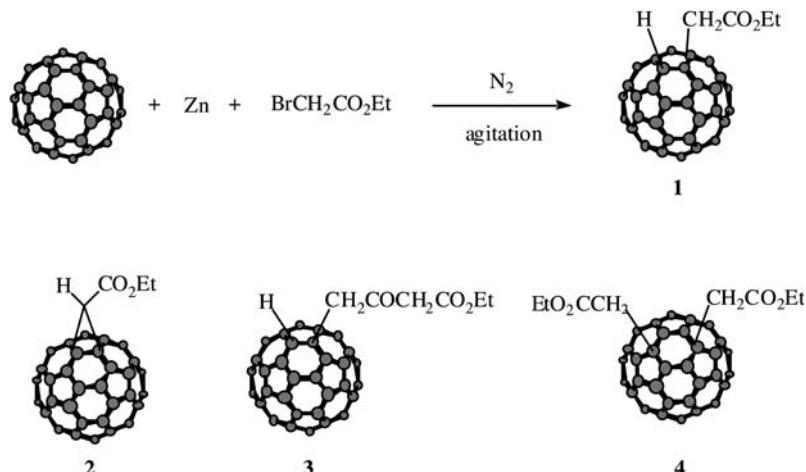
Heating a deoxygenated sample of crystalline **2** at 180 °C for 10 min afforded 48% each of the fullerene **1** and the antipodal bisadduct **3** (96% conversion; no other components detected). The bisadduct **3** was isolated and its structure confirmed by NMR spectroscopy and FAB mass spectrometry, as well as by single crystal structure analysis.

References: B. Krautler, T. Muller, J. Maynollo, K. Gruber, C. Kratky, P. Ochsenbein, D. Schwarzenbach, H.-B. Burgi, *Angew. Chem. Int. Ed. Engl.*, **35**, 1204 (1996); Y. Murata, N. Kato, K. Fujiwara, K. Komatsu, *J. Org. Chem.*, **64**, 3483 (1999).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: [60]fullerene, zinc, ethyl bromoacetate, 1-ethoxycarbonylmethyl-1,2-



dihydro[60]fullerene

Experimental procedures:

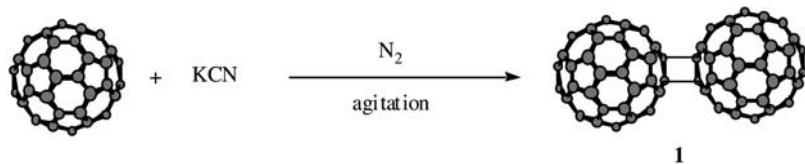
In the nitrogen bag, 50.2 mg of [60]fullerene, ethyl bromoacetate (5 equiv.), zinc dust (20 equiv.) and the stainless-steel ball were placed in the capsule. The above mixture was vigorously agitated for 20 min at room temperature, quenched with 0.5 mL of $\text{CF}_3\text{CO}_2\text{H}$ in 20 mL of *o*-dichlorobenzene, and carefully separated by silica gel chromatography with hexane-toluene as the eluent to give the expected adduct **1** (17.2%) (62.5% based on consumed C₆₀) together with **2** (0.8%), **3** (3.9%), **4** (1.8%) and unreacted C₆₀ (72.5%).

References: G. Wang, Y. Murata, K. Komatsu, T.S.M. Wan, *Chem. Commun.*, 2059 (1996); T.-H. Zhang, G.-W. Wang, O. Lu, Y.-J. Li, R.-F. Peng, Y.-C. Liu, Y. Murata, K. Komatsu, *Org. Biomol. Chem.*, **2**, 1698 (2004).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: C60, KCN, [2+2]cycloaddition, C120



Experimental procedures:

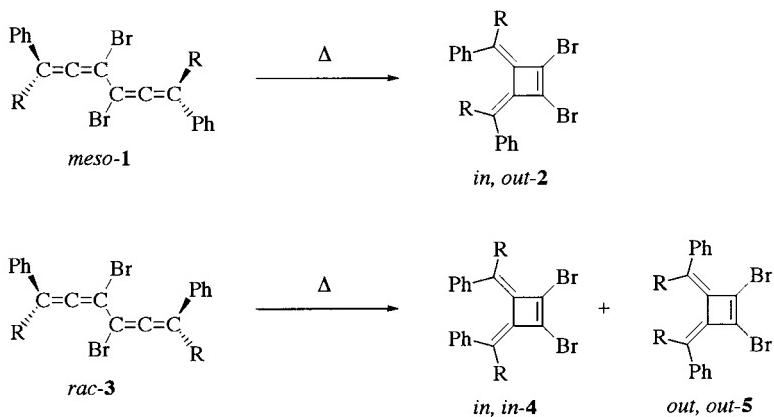
A mixture of C60 and 20 molar equiv. of KCN powder was vigorously vibrated for 30 min under nitrogen according to our previous procedure. Analysis by high-performance liquid chromatography of the reaction mixture dissolved in *o*-dichlorobenzene (ODCB) on a Cosmosil Buckyprep column with toluene as the eluent showed only one major product besides unchanged C60. Separation by flash chromatography on silica gel, eluted with hexane-toluene and then with toluene-ODCB, gave 70% of recovered C60 and 18% of C120 (**1**).

References: G. Wang, K. Komatsu, Y. Murata, M. Shiro, *Nature*, **387**, 583 (1997).

Type of reaction: C–C bond formation

Reaction condition: solid state

Keywords: *trans*-diallene, [2+2]conrotatory cyclization, dimethylenecyclobutene



Experimental procedures:

Compound **1** (0.2 g) was heated in the crystalline state at 135 °C for 1.5 h to give **2** (0.2 g, 100% yield) as colorless needles after recrystallization from AcOEt (mp 214–215 °C).

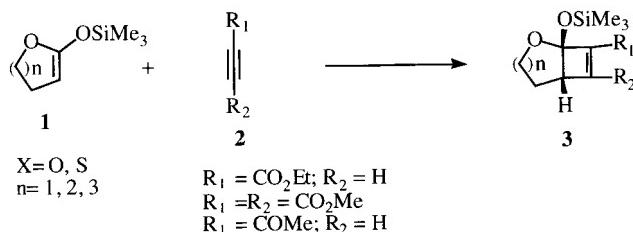
Compound **3** (0.4 g) was heated in the crystalline state at 125 °C for 1.5 h to give a 1:1 mixture of **4** and **5** (0.4 g, 100% yield). Fractional recrystallization of the mixture gave pure **4** as colorless needles (mp 180–183 °C) and pure **5** as colorless needles (mp 215–218 °C).

References: F. Toda, K. Tanaka, T. Tamashima, M. Kato, *Angew. Chem. Int. Ed. Engl.*, **37**, 2724 (1998).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: ketene silyl acetale, alkine, [2+2]cycloaddition, cyclobutane

**Experimental procedures:**

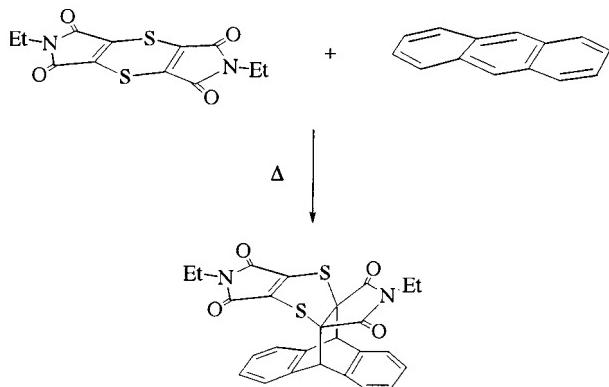
To the ketene silyl (thio)acetal (1 equiv.) was added at room temperature neat ethyl propynoate, dimethyl acetylenedicarboxylate or ethynyl methyl ketone (1 equiv.). The mixture was stirred for 5 h at room temperature. The volatile products were removed at room temperature in vacuo (0.1 Torr) for 30 min. Purification of the crude reaction mixture by silica gel column chromatography (ethyl acetate-hexane, 5:95) afforded cycloadducts.

References: M. Miesch, F. Wendling, *Eur. J. Org. Chem.*, 3381 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 1,4-dithiin, anthracene, Diels-Alder reaction, single-crystal-to-single-crystal transformation



Experimental procedures:

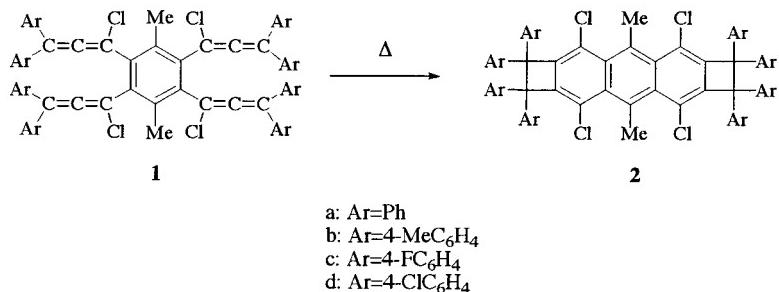
The charge-transfer crystal of 1,4-dithiin and anthracene was grown in dichloromethane solution (50 mM) by slow evaporation of solvent at low temperature (-4°C). After one week, a brown single crystal was isolated. The solid-state reaction of the anthracene-1,4-dithiin CT crystals was carried out at four temperatures (viz. 50, 60, 70 and 80°C), and the conversion was monitored by ^1H NMR spectroscopy.

References: J. H. Kim, S. M. Hubig, S. V. Lindeman, J. K. Kochi, *J. Am. Chem. Soc.*, **123**, 87 (2001); J. H. Kim, S. V. Lindeman, J. K. Kochi, *ibid.* **123**, 4951 (2001).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: allene, thermal cycloaddition, cyclobutane, anthrocyclobutene



Experimental procedures:

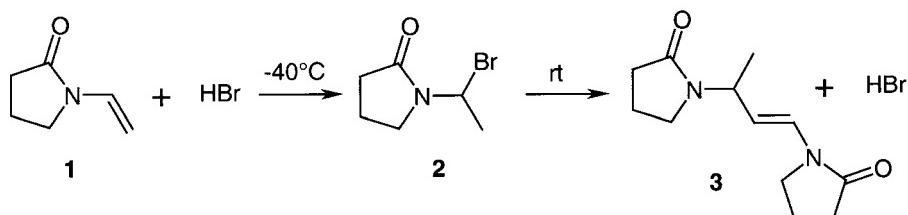
Compound **1a** (0.5 g) was heated in the crystalline state at 180 °C on a hot plate for 30 min to give **2a** (0.5 g, 100% yield) as yellow prisms (mp >300 °C).

References: K. Tanaka, N. Takamoto, Y. Tezuka, M. Kato, F. Toda, *Tetrahedron*, **57**, 3761 (2001).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *N*-vinylpyrrolidene, acid catalysis, linear dimerization, gas-solid reaction

**Experimental procedure:**

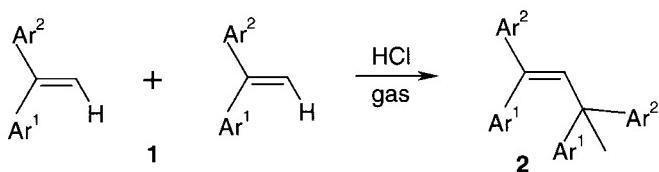
N-Vinylpyrrolidone **1** (1.00 g, 9.0 mmol) was spread on cylindric glass rings (Raschig coils) in a 500-mL flask and crystallized by cooling to -40°C in a vacuum. HBr gas (1 bar) was applied for 2 h at that temperature. Excess gas was pumped off to a recipient at -196°C for further use and the solid reaction product **2** was left at room temperature with repeated evacuation for removal of the liberated HBr. The racemic product **3** was recrystallized from acetone to yield 650 mg (65%) of the pure compound (mp 70–73 °C) that was spectroscopically characterized.

References: G. Kaupp, D. Matthies, *Chem. Ber.*, **120**, 1897 (1987).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 1,1-diarylethylene, HCl, catalysis, linear dimerization, head-to-tail, waste free, gas-solid reaction, 1,1,3,3-tetraaryl-1-butene



- a: Ar¹=Ar²=Ph (-50°C; 100%)
- b: Ar¹=Ph, Ar²=*p*-Tol (-25°C; 100%; E/Z=33:67)
- c: Ar¹=Ar²=*p*-Tol (-25°C; 100 %)
- d: Ar¹=Ph, Ar²=*p*-Anis (-25°C; 100%; E/Z=15:85)
- e: Ar¹=*p*-Tol; Ar²=*p*-Anis (-25°C; 100%; E/Z=52:48)

Experimental procedures:

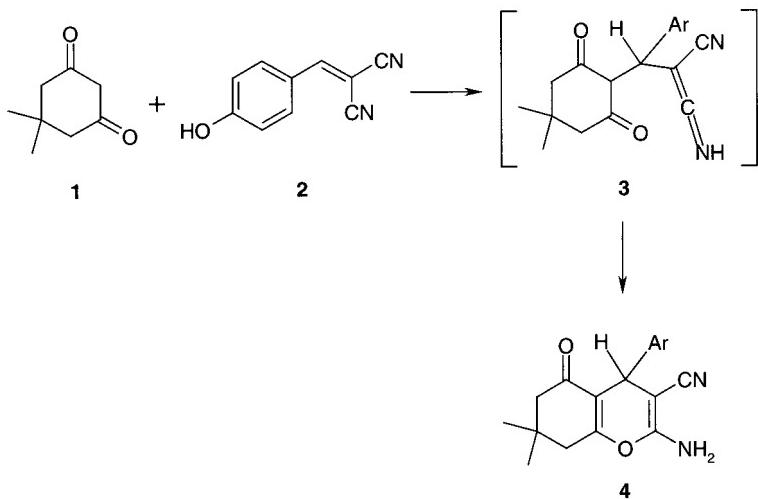
The 1,1-diarylethylene **1** (1.00 g) was crystallized in a 100-mL flask by cooling to the appropriate temperature in a vacuum and HCl gas (1 bar) was added and left at that temperature overnight. The pure products **2** were obtained after removal of the HCl gas and thawing up to room temperature.

References: G. Kaupp, A. Kuse, *Mol. Cryst. Liq. Cryst.*, **313**, 361 (1998).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: arylidene malodinitrile, dimedone, Michael addition, cyclization, pyrane



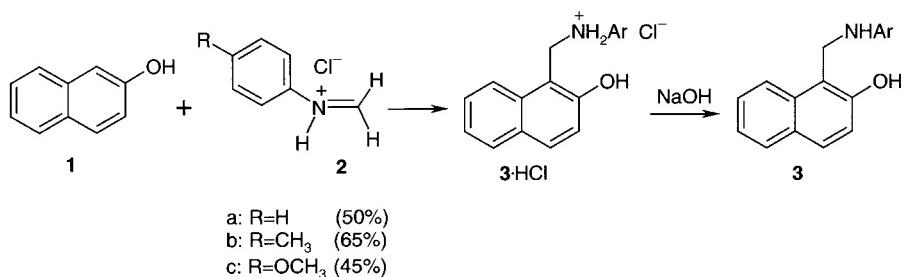
Experimental procedure:

A mixture of dimedone **1** (2.00 mmol) and **2** (2.00 mmol) was ball-milled at 70 °C for 1 h to give an 80% conversion to **4**. Completion of the reaction was achieved by heating the yellow powder to 100 °C for 2 h. The yield was 620 mg (100%) of **4**, mp 222–223 °C.

References: G. Kaupp, M.R. Naimi-Jamal, J. Schmeyers, *Tetrahedron*, **59**, 3753 (2003).

Type of reaction: C–C bond formation**Reaction condition:** solvent-free

Keywords: 2-naphthol, methyleneimine, aminomethylation, solid-solid reaction, 1-(N-arylaminoethyl)-2-naphthol

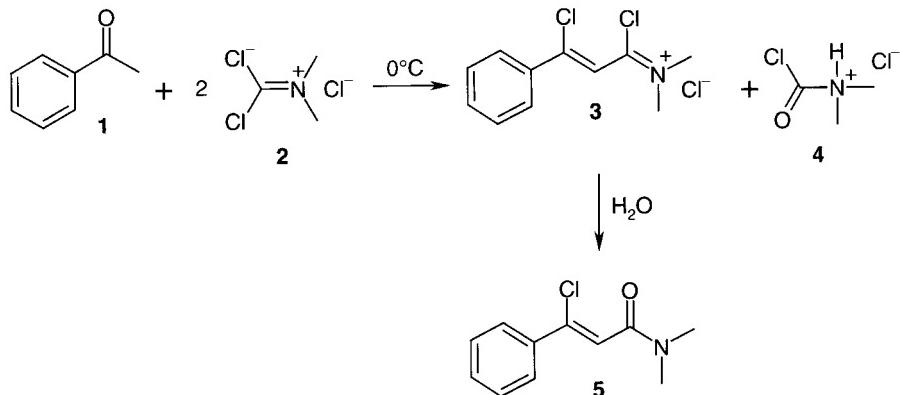
**Experimental procedures:**

The arylmethene imine hydrochloride **2** was sampled under dry argon, precisely weighed (ca. 2 mmol) and ball-milled with the equivalent of 2-naphthol **1** for 1 h. The solid-solid character was finally lost during the reaction as the material became sticky. The free base **3** was obtained after neutralization of **3·HCl** in CH₂Cl₂ by washing with NaHCO₃ solution and crystallization from ethanol.

References: G. Kaupp, J. Schmeyers, J. Boy, *J. Prakt. Chem.*, **342**, 269 (2000).

Type of reaction: C–C bond formation**Reaction condition:** solid-state

Keywords: Viehe salt, acetophenone, solid-solid reaction, cinnamamide

**Experimental procedure:**

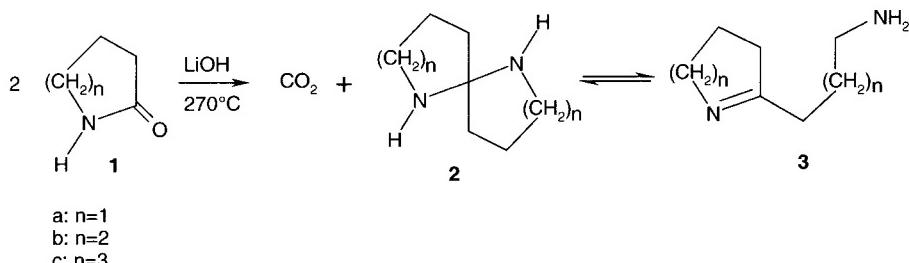
Acetophenone **1** (600 mg, 5.00 mmol) was cooled to 0°C in a 10-mL milling beaker and Viehe salt **2** (815 mg, 5.00 mmol) was added unter N₂. Ball-milling at 0°C was performed for 2 h. A solid mixture of product **3** and couple product **4** was quantitatively obtained. Compound **5** was obtained by treatment with water, filtration and drying.

References: G. Kaupp, J. Boy, J. Schmeyers, *J. Prakt. Chem.*, **340**, 346 (1998).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: lactam, base catalysis, complex reaction, spiroaminal, aminoalkylimin

**Experimental procedures:**

Valerolactam **1b** (10 g, 100 mmol) and LiOH·H₂O (4.25 g, 100 mmol) were heated to 200°C to remove water, then under N₂ to 270°C for 4 h under reflux. The product **2b** and residual **1** were distilled off while the temperature was in-

creased up to 320 °C. The raw material of two runs was separated by fractionation at a heatable 80-cm spinning band column under vacuum. Pure **2b** (7.6 g, 54%; bp₁₄ 84 °C) was obtained as a useful precursor for diaziridine synthesis.

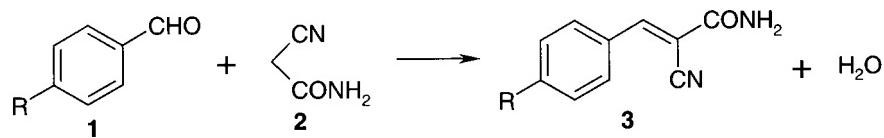
Pyrrolidon **1a** (8.51 g, 100 mmol) or caprolactam **1c** (11.30 g, 100 mmol) and LiOH·H₂O (4.25 g, 100 mmol) were dissolved in water (30 mL) and evaporated to dryness in order to get a homogeneous mixture that was heated under N₂ to 270 °C for 4 h under reflux, then distilled over and pure **3a** (88%, bp₁₄ 83 °C) or **3c** (55%, bp₁ 94 °C) was obtained by spinning band column distillation.

References: S.N. Denisenko, E. Pasch, G. Kaupp, *Angew. Chem.*, **101**, 1397 (1989); *Angew. Chem. Int. Ed. Engl.*, **28**, 1381 (1989).

Type of reaction: C–C bond formation

Reaction condition: solvent-free or solid-state

Keywords: cyanoacetamide, malodinitril, methyl cyanoacetate, aromatic aldehyde, Knoevenagel condensation, solid-solid reaction, base catalysis, melt reaction, uncatalyzed, cinnamamide, cinnamonitril, methyl cinnamate

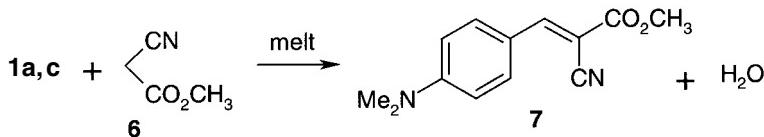
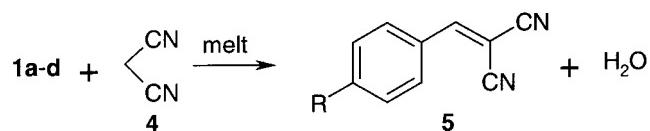


a: R=OH

b: R=Cl

c: R=NMe₂

d: R=H



Experimental procedures:

3 (catalyzed): Cyanoacetamide **2** (2.00 mmol) and aldehyde **1** (2.00 mmol) were ball-milled for 10 min. The powder was transferred to a 250-mL flask that was evacuated and filled with trimethylamine gas and left for 24 h for the completion of the reaction. The gaseous base catalyst and the water of reaction were evacuated and a quantitative yield of pure **3a-c** obtained.

3 (uncatalyzed): Equimolar mixtures of **1** and **2** were heated to 170 °C (**1d** and **2** to 100 °C) for 1 h to obtain **3a** (100%), **3b** (100%), **3c** (87%), or **3d** (92%). **3c, d** were recrystallized from ethanol.

5 (uncatalyzed): Malodinitril **4** (2.00 mmol) and aldehyde **1** (2.00 mmol) were heated to 150 °C for 1 h to obtain **5a** (100%), **5b** (100%), or **5c** (100%). **5d** was quantitatively obtained as a yellow powder by ball-milling of an initially liquid 1:1 mixture of **1d** and **4** (3.00 mmol) for 1 h.

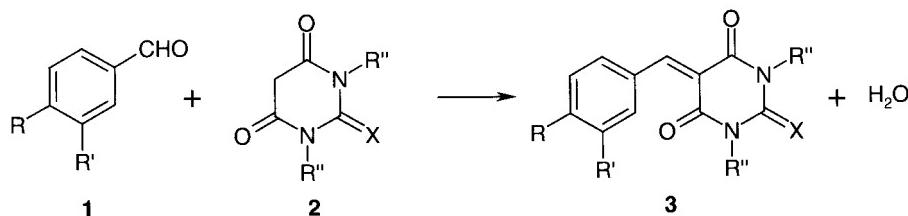
7 (uncatalyzed): Methyl cyanoacetate (**6**) (2.00 mmol) and aldehyde **1a** and **1c** (2.00 mmol) were heated to 170 °C for 1 h to obtain pure **7a** and **7c** in quantitative yield.

References: G. Kaupp, M.R. Naimi-Jamal, J. Schmeyers, *Tetrahedron*, **59**, 3753 (2003).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: aromatic aldehyde, barbituric acid, Knoevenagel condensation, uncatalyzed, large scale



a: R=NMe₂, R'=H, R''= Et, X=S (rt, 1 h)

b: R=OH, R'=H, R''= Me, X=O (rt, 1 h)

c: R=OH, R'=OMe, R''= H, X=O (50 °C, 1 h)

d: R=OH, R'= R''= H, X=O (from rt to 50 °C, 3 h)

e: R=R'=H, R''=Me, X=O (rt, 1 h; initially partly liquid, becomes solid)

Experimental procedures:

Large scale: A stoichiometric mixture of **1b** and **2b** (200 g per batch) was milled in a water cooled (14 °C) horizontal ball-mill (2 L Simoyer[®], Zoz GmbH) with 2 kg steel balls (5 mm diameter) for 1 h at 1000 rpm. The product **3b** was milled out at 600–1000 rpm. 100% yield (recovery) was obtained in the second batch etc. The purity of **3b** was checked by IR, ¹H, ¹³C NMR and mp (297 °C) after drying in a vacuum at 80 °C.

Similarly, **1d** and **2d** reacted with quantitative yield in the 2-L ball-mill that was not water cooled while care was taken that the interior temperature did not rise above 50 °C (1 h per 200 g batch). Mp 299–301 °C.

Small scale: *p*-Dimethylaminobenzaldehyde **1a** (2.00 mmol) and the thiobarbituric acid **2a** (2.00 mmol) or **1c** (2.00 mmol) and **2c** (2.00 mmol) were ball-milled at room temperature or 50 °C for 1 h or 3 h, to give quantitative yields of **3a** (mp 207–209 °C) or **3c** (mp 313 °C) after drying at 80 °C in a vacuum.

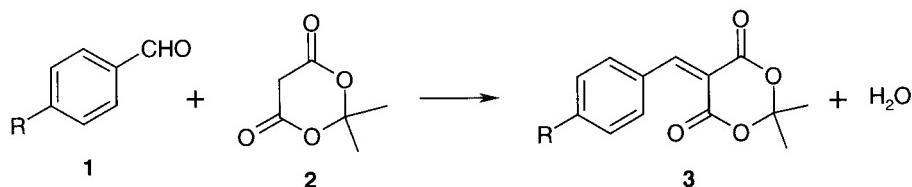
Liquid-solid: Benzaldehyde **1e** (212 mg, 2.00 mmol) and **2b** (2.00 mmol, poorly soluble in **1e**) were ball-milled at room temperature for 1 h. The solid product was dried at 80 °C in a vacuum to give **3e** (100%). **3e** (mp 260–261 °C) was recrystallized from ethanol.

References: G. Kaupp, M.R. Naimi-Jamal, J. Schmeyers, *Tetrahedron*, **59**, 3753 (2003).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: aromatic aldehyde, Meldrum's acid, Knoevenagel condensation, uncatalyzed



a: R=OH
b: R=NMe₂

Experimental procedures:

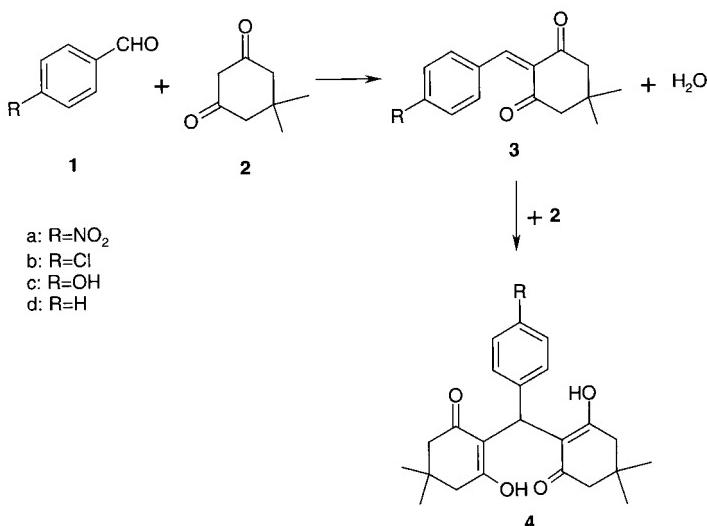
Meldrum acid **2** (288 mg, 2.00 mmol) and aldehyde **1** (2.00 mmol) were co-ground and heated to 50 °C when **3a, b** crystallized after intermediate melting. The quantitatively obtained pure product **3a, b** was dried at 80 °C in a vacuum. Mp 193 °C and 162 °C.

References: G. Kaupp, M.R. Naimi-Jamal, J. Schmeyers, *Tetrahedron*, **59**, 3753 (2003).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: dimedone, aromatic aldehyde, Knoevenagel condensation, Michael addition, uncatalyzed



Experimental procedures:

Dimedone **2** (4.00 mmol) and aldehyde **1** (2.00 mmol) were co-ground in a mortar and heated to 80 °C for 3 h (**1a**, **1b**) or for 1 h (**1c**). The product **4** crystallized quantitatively from an intermediate melt and was obtained in pure form. Mp 189 °C, 139 °C and 189 °C.

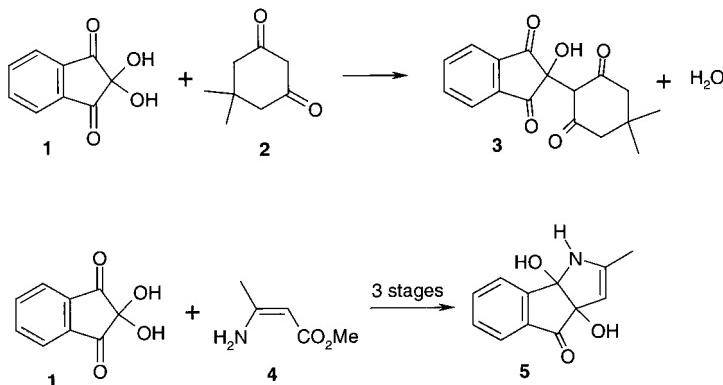
Compound **4d** was quantitatively obtained from an initially liquid 2:1 mixture of **2** and **1d** at 100 °C for 90 min and drying at 80 °C in a vacuum. Equimolar mixtures of **2** and **1c** or **1d** did not provide compound **3c, d** under the reaction conditions but provided **4c, d** and unreacted **1c, d**.

References: G. Kaupp, M.R. Naimi-Jamal, J. Schmeyers, *Tetrahedron*, **59**, 3753 (2003).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: ninhydrin, dimedone, aminocrotonate, condensation, cyclization, cascade reaction, waste-free, solid-solid reaction

**Experimental procedures:**

Preparation of 3: Ninhydrin **1** (178 mg, 1.00 mmol) and dimedone **2** (140 mg, 1.00 mmol) were ball-milled for 1 h at room temperature. Pure **3** (300 mg, 100%) was obtained. Mp 193–195 °C (decomp.).

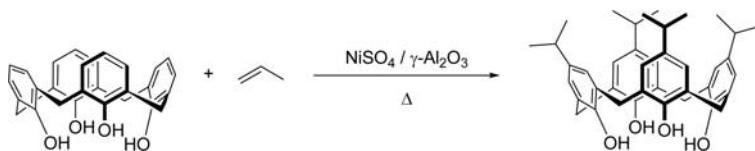
Preparation of 5: Ninhydrin **1** (356 mg, 2.00 mmol) and 3-aminocrotonate **4** (230 mg, 2.00 mmol) were ball-milled for 1 h at room temperature. Pure **5** (545 mg, 99%) was obtained after drying in a vacuum at 80 °C. Mp 201–202 °C.

References: G. Kaupp, M.R. Naimi-Jamal, J. Schmeyers, *Chem. Eur. J.*, **8**, 594 (2002).

Type of reaction: C–C bond formation

Reaction condition: gas-solid

Keywords: alkylation, *p*-iso-propylcalix[4]arene

**Experimental procedures:**

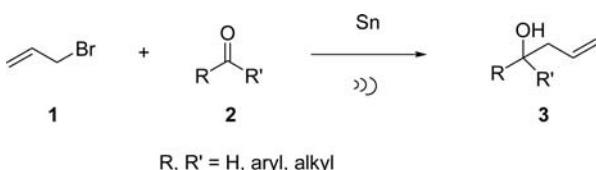
A mixture of calix[4]arene (500 mg, 1.18 mmol) and of catalyst (1.5 g) was ground into a homogeneous powder and then charged into a tubular reactor. Under atmospheric pressure the reactor was heated in an oven at 250 °C under a circulation of propylene (50 mL min⁻¹). After the desired reaction time (3 h for instance), the reactor was cooled and the crude reaction mixture extracted with hot chloroform.

References: B. Yao, J. Bassus, R. Lamartine, *New J. Chem.*, **20**, 913 (1996).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: tin, homoallylation, ultrasonic irradiation



Experimental procedures:

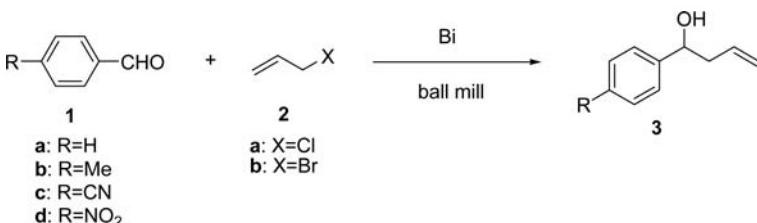
A typical experiment involved the addition of the carbonyl compound (5 mmol) to a suspension of allyl bromide (20 mmol) and commercially available Sn powder (5 mmol) in a stoppered, 50-mL, round-bottomed flask. This suspension was then allowed to react under sonication for 12 h before being quenched with water (ca. 0.5 ml) and extracted with Et_2O (3×15 mL). The products were analyzed by ^1H NMR and GC-MS.

References: P.C. Andrews, A.C. Peatt, C.L. Raston, *Tetrahedron Lett.*, **43**, 7541 (2002).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Barbier-type allylation, bismuth, homoallyl alcohol



Experimental procedures:

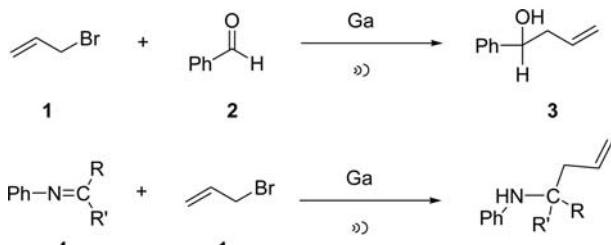
4-Nitroacetophenone (43.1 mg, 0.26 mmol), allyl bromide (45.3 mg, 0.37 mmol), bismuth shot (203 mg), and two stainless steel balls were placed in a stainless steel vial with a screw cap. The reaction vessel was shaken using a ball mill apparatus at a rate of 30 Hz. After 0.5 h, milling was stopped and the resulting pasty solid was first triturated with 0.1 M HCl and then extracted with EtOAc . Extraction with EtOAc alone led to a diminished yield of the product. The organic phase was separated, filtered on a thin Celite bed, and evaporated to leave a pale yellow oil, which was chromatographed on silica gel using hexane- EtOAc as the eluent to give 2-(4-nitrophenyl)pent-4-en-2-ol (37.7 mg, 70%) as an oil.

References: S. Wada, N. Hayashi, H. Suzuki, *Org. Biomol. Chem.*, **1**, 2160 (2003).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: gallium metal, homoallylic alcohol, homoallylic amine, sonication



R,R' = alkyl, aryl or H

Experimental procedures:

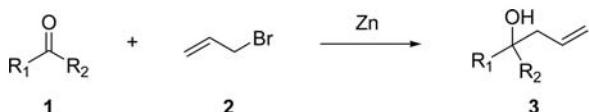
In a Schlenk flask under a nitrogen atmosphere, a suspension of 5 mmol (0.35 g) of gallium metal and 5 mmol (0.53 g) of benzaldehyde was allowed to react via sonication for 12 h, resulting in the production of a brown oil and the complete consumption of the gallium metal. This was then quenched with 0.5 mL of H₂O. The reaction mixture was extracted with 3×10 ml of diethyl ether, with the ethereal layers being combined and dried over MgSO₄. The solution was then filtered and concentrated under reduced pressure, to give a colorless oil. The homoallylic alcohol was isolated in 97% yield by flash chromatography on silica gel using a 10:1 ratio of hexane to ethyl acetate.

References: P.C. Andrews, A.C. Peatt, C.L. Raston, *Tetrahedron Lett.*, **45**, 243 (2004).

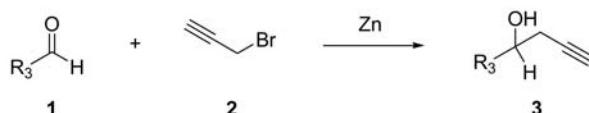
Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: homoallyl alcohol, homopropargyl alcohol, zinc powder



- | | |
|--|--|
| a: R ¹ = Ph; R ² = H | g: R ¹ = Ph; R ² = Me |
| b: R ¹ = 2-ClC ₆ H ₄ ; R ² = H | h: R ¹ = Ph; R ² = Ph |
| c: R ¹ = 4-BrC ₆ H ₄ ; R ² = H | i: R ¹ = Ph; R ² = Et |
| d: R ¹ = 4-MeOC ₆ H ₄ ; R ² = H | j: R ¹ = C ₅ H ₁₁ ; R ² = Me |
| e: R ¹ = 3-MeOC ₆ H ₄ ; R ² = H | k: R ¹ , R ² = -(CH ₂) ₅ ⁻ |
| f: R ¹ = Me(CH ₂) ₃ CH ₂ ; R ² = H | l: R ¹ , R ² = -(CH ₂) ₄ ⁻ |



- | | |
|--|---|
| a: R ³ = Ph | e: R ³ = 3-MeOC ₆ H ₄ |
| b: R ³ = 2-ClC ₆ H ₄ | f: R ³ = 2,4-Cl ₂ C ₆ H ₄ |
| c: R ³ = 3-BrC ₆ H ₄ | g: R ³ = 2-MeOC ₆ H ₄ |
| d: R ³ = 4-MeOC ₆ H ₄ | h: R ³ = 4-ClC ₆ H ₄ |

Experimental procedures:

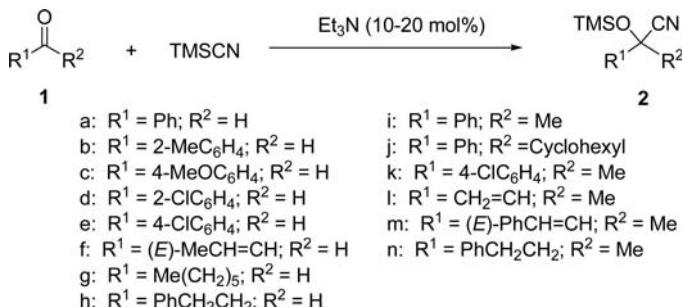
Activated zinc powder (0.52 g, 8 mmol) was placed in a flame-dried 50-mL round-bottom flask fitted with a magnetic stir bar. Then aldehyde (7 mmol) and allyl bromide (0.96 g, 8 mmol) were added via a dropping funnel. The resulting mixture was vigorously stirred at room temperature. After reaction was completed, saturated NH₄Cl solution was added and the organic layer was separated and dried over anhydrous MgSO₄. The residue was purified by flash chromatography on silica gel using petroleum ether-EtOAc (15:1) as the eluent. This afforded the corresponding homoallylic alcohols.

References: J.-X. Wang, X. Jia, T. Meng, L. Xin, *Synthesis*, 2838 (2005).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: cyanohydrins, trimethylsilyl cyanide, *O*-acyl cyanohydrine

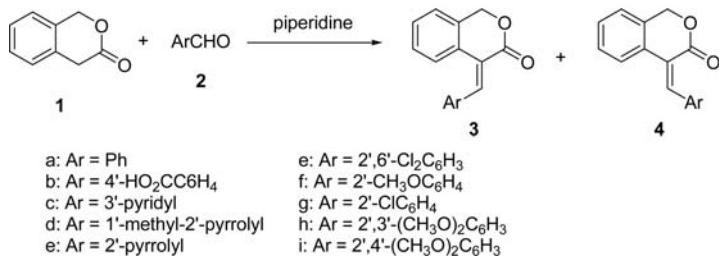
**Experimental procedures:**

In a round-bottomed flask were placed the carbonyl compound (0.5 mmol) and Et₃N (10–40 mol%) and the mixture was stirred at room temperature. The cyanide source (1.1–2 equiv.) was slowly added at the same temperature. When the reaction was judged to be complete (¹H NMR or GC), the Et₃N was evaporated under vacuum, giving a residue which, generally, did not require any further purification. In a few cases, this residue had to be purified by flash chromatography eluting with mixtures of *n*-hexane-EtOAc.

References: A. Baeza, C. Nájera, M. de G. Retamosa, J.M. Sansano, *Synthesis*, 2787 (2005).

Type of reaction: C–C bond formation**Reaction condition:** solvent-free

Keywords: (E)- and (Z)-4-(aryl methylene)-3-isochromanone, Knoevenagel condensation

**Experimental procedures:**

A mixture of 3-isochromanone (6.75 mmol), the appropriate aldehyde (6.75 mmol) and five drops of piperidine was stirred at 140 °C under argon for 1 h. The mixture was allowed to cool to room temperature and the oily residue was crystallized from ethanol. A second recrystallization from methanol gave

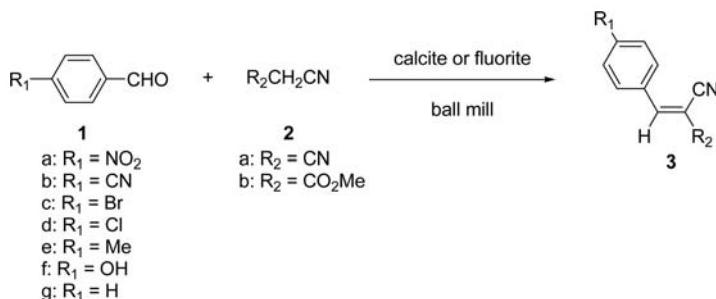
pure products. In some cases the products were purified by column chromatography.

References: T. Lórónd, P. Forgó, A. Földesi, E. Ósz, L. Prókai, *Eur. J. Org. Chem.*, 2996 (2002).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Knoevenagel condensation, calcite, fluorite



Experimental procedures:

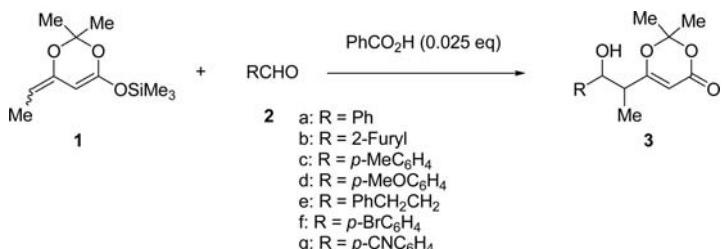
Malononitrile (33.7 mg; 0.510 mmol), 4-nitrobenzaldehyde (38.5 mg, 0.255 mmol), calcite grains (19.5 mg, 1–4 mm in size), and two stainless balls of 7 mm diameter were placed in a stainless cylinder (1.2×4 cm²; 5 mL volume) with a screw cap. The cap was tightened and the reaction vessel was shaken using a ball mill apparatus (Retsch mixer mill, MM200; Retsch GmbH, Haan, Germany) at a rate of 30 Hz. The vessel warmed slightly by mechanical friction. After 0.5 h, milling was stopped and the resulting slightly yellow solid was extracted with ethyl acetate by trituration. The extract was filtered on a thin Celite bed and evaporated to leave a pale yellow solid which was recrystallized from ethanol to give pure 4-nitrobenzylidenemalononitrile (48.8 mg, 96%) as pale yellow crystals, mp 160–162 °C.

References: S. Wada, H. Suzuki, *Tetrahedron Lett.*, **44**, 399 (2003).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: 2,2-dimethyl-[1,3]-dioxin-4-one, Mukaiyama aldol reaction

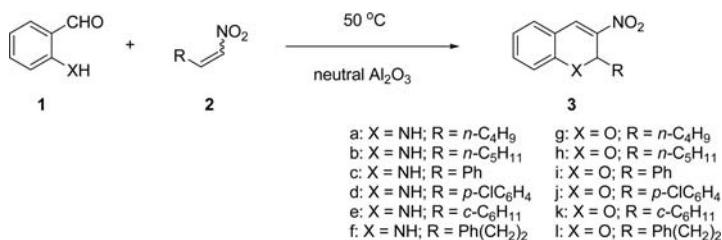
**Experimental procedures:**

In a dried vial **1** (2 equiv., 1 mmol), benzoic acid (0.025 equiv) and aldehyde (1 equiv., 0.5 mmol) were mixed and stirred at 20 °C. The reaction was quenched with water (2 mL) and the organic layer extracted in Et₂O (3 × 5 mL). The crude product was desilylated by Kruger and Carreira's procedure and the resulting mixture purified by silica gel chromatography (eluent: CHCl₃–Et₂O 9/1).

References: M.R. Acocella, A. Massa, L. Palombi, R. Villano, A. Scettri, *Tetrahedron Lett.*, **46**, 6141 (2005).

Type of reaction: C–C bond formation**Reaction condition:** solvent-free

Keywords: alumina, 3-nitro-1,2-dihydroquinoline, 3-nitrochromene

**Experimental procedures:**

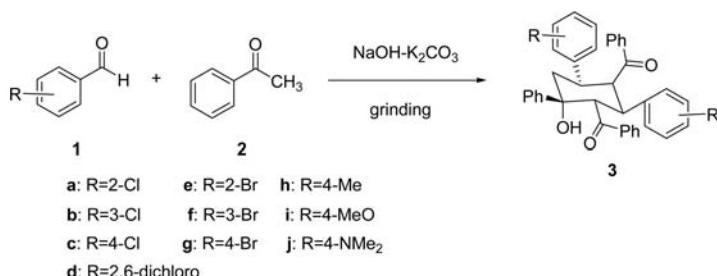
To a stirred heterogeneous mixture of neutral alumina (1 g) and 2-aminobenzaldehyde (1 mmol) was added 1 mmol of the appropriate nitroalkane and the obtained mixture was warmed at 50 °C under stirring for 1.5 h. Then, the mixture was cooled at room temperature and directly charged onto a chromatography column to give the pure product.

References: R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, *Green Chem.*, **7**, 825 (2005).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: 1,2,3,4,5-pentasubstituted cyclohexanol, acetophenone



Experimental procedures:

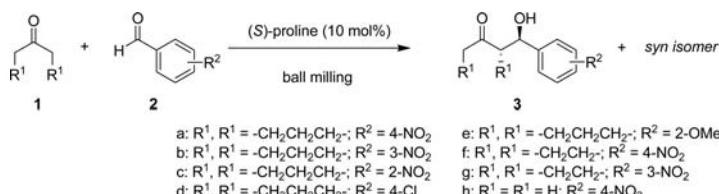
NaOH (50 mmol) was mixed with K₂CO₃ (25 mmol) and ground finely. To the fine powder was added a mixture of 2-chlorobenzaldehyde (50 mmol) and acetophenone (0.55 mmol) and this was ground at room temperature till the liquid disappeared (over 15 min) to furnish an incompact, white solid powder. After treatment with water and recrystallization in toluene, a white solid of 2,4-dibenzoyl-3,5-di(2-chlorophenyl)-1-phenylcyclohexanol was obtained, mp 208–210°C, 95% yield.

References: X. Luo, Z. Shan, *Tetrahedron Lett.*, **47**, 5623 (2006).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: aldol reaction, ball mill, proline, quinidine



Experimental procedures:

A reaction vessel was charged with aldehyde **1** (2.0 mmol, 1.0 equiv.), ketone **2** (2.2 mmol, 1.1 equiv.), and (S)-proline (23 mg, 0.2 mmol, 0.1 equiv.). Stirring was either started in a grinding bowl using the ball mill with a rotation speed of 250–400 rpm, or in a round-bottomed flask using a conventional magnetic stirring bar. After an appropriate reaction time, the crude product was washed off

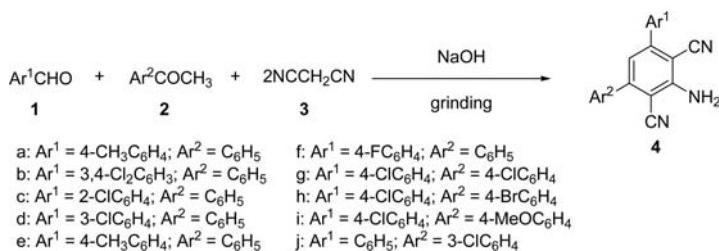
the reaction vessel with Et₂O (4×40 mL), and the combined organic fractions were filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (pentane/EtOAc, 100:0–80:20) afforded the pure aldol product **3a–h**.

References: B. Rodríguez, T. Rantanen, C. Bolm, *Angew. Chem. Int. Ed.*, **45**, 6924 (2006).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: three-component condensation, 2,6-dicyanoaniline



Experimental procedures:

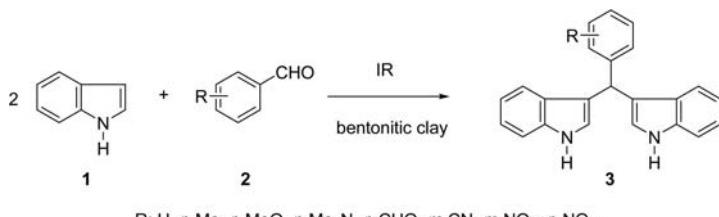
Aromatic aldehyde **1** (2 mmol), aromatic ketone **2** (2 mmol), malononitrile **3** (5 mmol), and NaOH (3 mmol) were added to a mortar. The mixture was ground with a pestle at room temperature. The reaction was completed in 3–5 min and the reaction mixture was poured into water. The product was filtered, dried, and recrystallized from 95% ethanol.

References: L. Rong, X. Li, H. Wang, D. Shi, S. Tu, *Chem. Lett.*, **35**, 1314 (2006).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: bentonitic clay, indole, diindolylmethane



Experimental procedures:

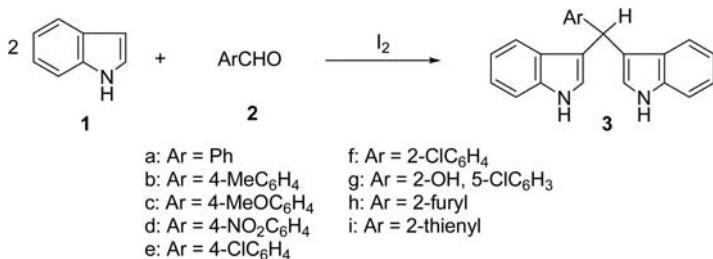
To a mixture of indole (1.0 g, 8.54 mmol) and benzaldehyde (0.45 g, 4.27 mmol) was added the bentonitic clay (4 g). The reaction mixture was irradiated with IR from a commercial IR lamp (250 W) for 15 min (after this reaction time no changes were detected by thin layer chromatography), and the temperature reached during the reaction was 180 °C. A 1:1 water-methanol mixture was then added to the produced reaction mixture for recrystallization purposes.

References: G. Penieres-Carrillo, J.G. Gracia-Estrada, J.L. Gutiérrez-Ramírez, C. Alvarez-Toledano, *Green Chem.*, **5**, 337 (2003).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: bis(indolyl)methane, iodine, indole

**Experimental procedures:**

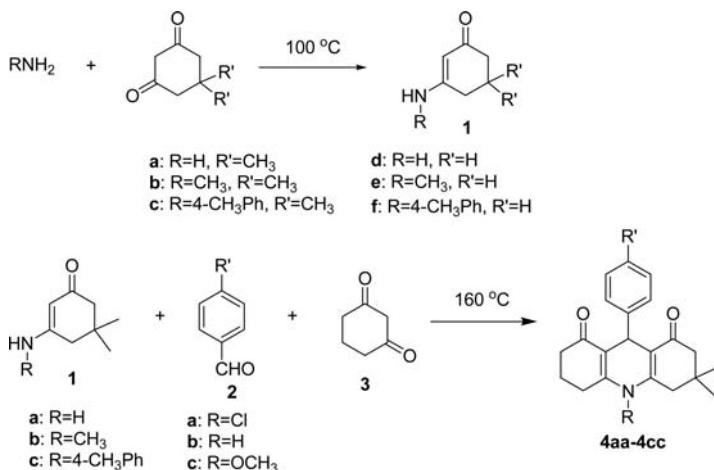
A mixture of benzaldehyde (1 mmol), indole (2 mmol) and I₂ (0.2 mmol) was ground in a mortar with a pestle at room temperature for several minutes. After completion of the reaction, as monitored by TLC, the mixture was treated with Na₂S₂O₃ to yield solid **3a**, which was purified by column chromatography (ethyl acetate : petroleum ether = 1 : 9) to afford the pure product (yield: 72%).

References: S.-J. Ji, S.-Y. Wang, Y. Zhang, T.-P. Loh, *Tetrahedron*, **60**, 2051 (2004).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: 4-arylacridinedione, 1,3-cyclohexanedione



Experimental procedures:

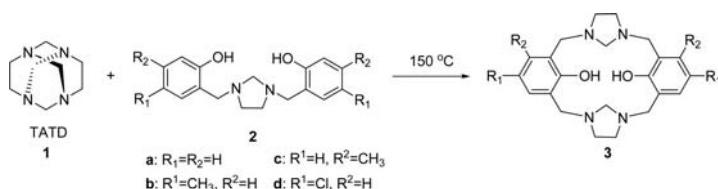
A mixture of an enaminone (**1a–c**, 0.5 mmol), and aromatic aldehyde (**2a–c**, 0.5 mmol) and 1,3-cyclohexanedione (56 mg, 0.5 mmol) was stirred at 160 °C for a desired time (monitored by TLC) in a preheated oil bath. After being cooled to room temperature, the reaction mixture was washed with ice-cold ethyl acetate (5 mL) to afford pure product (**4aa–cc**). The desired products of very high purity were achieved by recrystallization from ethanol.

References: G.-W. Wang, C.-B. Miao, *Green Chem.*, **8**, 1080 (2006).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Mannich-type reaction, heterocalixarene



Experimental procedures:

A TATD (1.0 g) and 1,3-bis(2'-hydroxy-benzyl)imidazoline **2** (6.0 mmol) mixture was heated to 150 °C with shaking until reaching melting point and then heated until solidification (3–20 min). The reaction mixture was left to cool to room temperature and then pulverized in a mortar. The obtained dust was suspended in

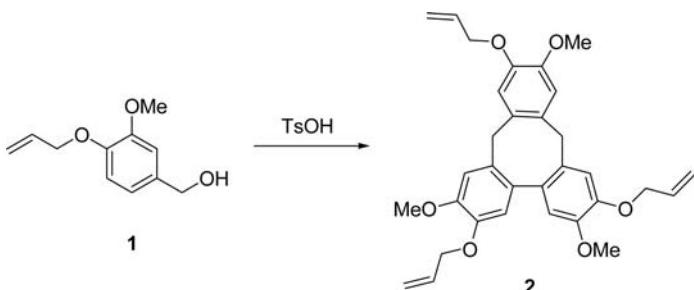
ethanol; the insoluble solid was separated by filtration, washed with water (3×5 mL) and then with ethanol (3×5 mL).

References: A. Rivera, R. Quevedo, *Tetrahedron Lett.*, **45**, 8335 (2004).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: cyclotrimeratrylene, grinding, 4-allyloxy-3-methoxybenzyl alcohol



Experimental procedures:

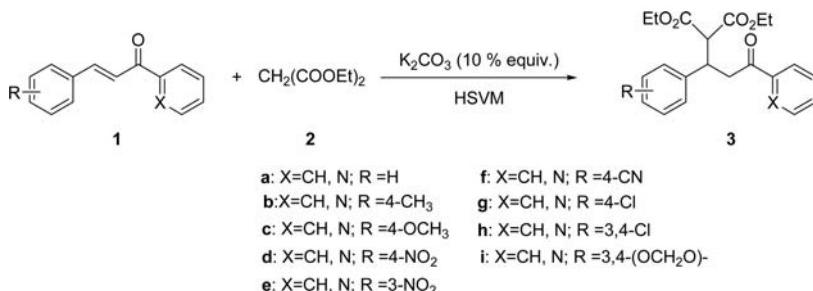
A total of 0.33 g (1.68 mmol) of 4-allyloxy-3-methoxybenzyl alcohol (**1**) and 0.32 g (1.69 mmol) of *p*-toluenesulfonic acid monohydrate were ground together to produce a sticky, pale brown syrup which solidified over a period of 2 days to yield tris-(*O*-allyl) cyclotrimeratrylene. The solid material was dissolved in dichloromethane, insoluble materials were removed by filtration, and the pure crystalline product was obtained by slow evaporation of the solvent. The white crystalline product (0.16 g, 54%) obtained proved to be pure tris-(*O*-allyl) cyclotrimeratrylene (**2**) when compared with authentic samples by melting point, TLC, and ^1H NMR analysis.

References: G. Rothenberg, A.P. Downie, C.L. Raston, J.L. Scott, *J. Am. Chem. Soc.*, **123**, 8701 (2001).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Michael addition, chalcone, azachalcone, mechanochemical reaction

**Experimental procedures:**

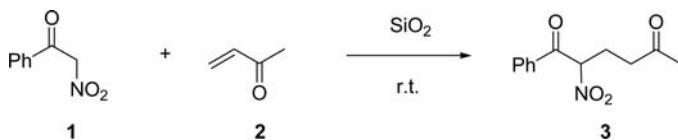
A mixture of compound **1** (0.1 mmol), diethyl malonate **2** (15.2 μL , 0.1 mmol) and K_2CO_3 (1.4 mg, 0.01 mmol) was vigorously shaken by HSVM for a designated time. The reaction mixture was collected and washed with water to remove the small amount of K_2CO_3 , and then dried to give the crude product **3**. The obtained product is essentially pure and can be further purified by crystallization from petroleum ether-EtOAc (10:1) at -20°C . Products **3c**, **3i** and **3m** were purified by column chromatography on silica gel with petroleum ether-EtOAc (5:1) as eluent.

References: Z. Zhang, Y.-W. Dong, G.-W. Wang, K. Komatsu, *Synlett*, 61 (2004).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Michael addition, α -nitro ketone, conjugated enone

**Experimental procedures:**

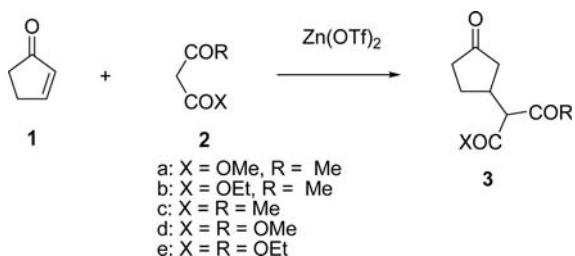
α -Nitro ketone **1** (1 mmol) was mixed with conjugated enone **2** (1 mmol), then, silica gel 60 (0.350 g, Merck 0.040–0.063 mm) was added. After mechanical stirring at room temperature for 30 min (until the starting materials were homogeneously adsorbed on the silica), the mixture was left at room temperature for the appropriate time (established by TLC or GC), then charged to a flash chromatography column, the column was eluted (EtOAc/cyclohexane, 2:8), affording the pure adduct **3**.

References: R. Ballini, D. Fiorini, M. V. Gil, A. Palmieri, *Green Chem.*, **5**, 475 (2003).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: β -dicarbonyl compound, conjugate-addition, dihydrofuran



Experimental procedures:

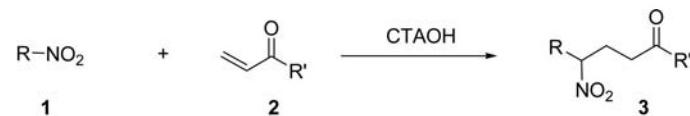
A mixture of the enone **1** (1.0 mmol), a Lewis acid (0.1 mmol) and a β -dicarbonyl compound **2** (2.0 mmol) was allowed to stand at room temperature until the reaction was completed. Then the reaction mixture was diluted with a suitable solvent (usually Et₂O/CH₂Cl₂), and the desired products were obtained in high chemical purity after a simple filtration through a short pad of silica gel. In some cases, the crude mixtures were directly chromatographed on silica gel using appropriate solvents.

References: A. Mekonnen, R. Carlson , *Eur. J. Org. Chem.*, 2005 (2006).

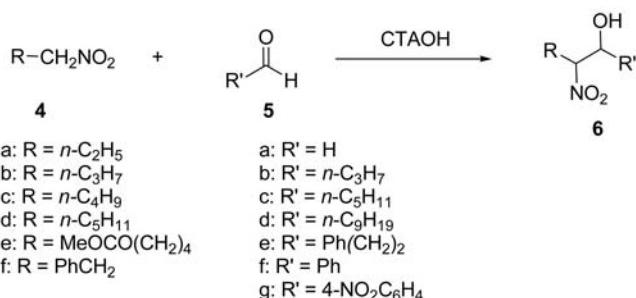
Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: cetyltrimethylammonium hydroxide, nitroalkane, Michael reaction, Henry reaction



- a: R = C₂H₅
 b: R = n-C₃H₇
 c: R = n-C₄H₉
 d: R = n-C₅H₁₁
 e: R = n-C₆H₁₃
 f: R = MeOCO(CH₂)₅
 g: R = MeCH(OH)(CH₂)₅



- a: R = n-C₂H₅
 b: R = n-C₃H₇
 c: R = n-C₄H₉
 d: R = n-C₅H₁₁
 e: R = MeOCO(CH₂)₄
 f: R = PhCH₂
 g: R' = 4-NO₂C₆H₄

Experimental procedures:

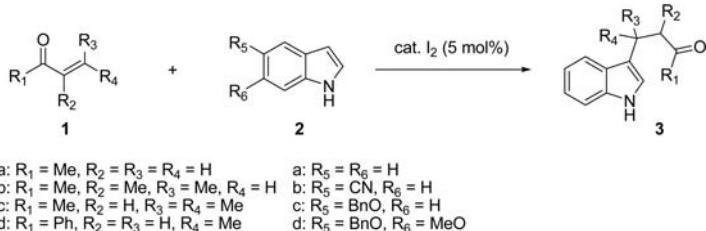
The Michael acceptor **2** (1 mmol) was added to a stirred mixture of nitrocompound **1** (1 mmol) in a 10% water solution of hexadecyltrimethyl ammonium hydroxide (CTAOH, 0.300 mL). The reaction progress was monitored by withdrawing aliquots which were analyzed by GC and TLC. The solution was then treated with brine (10 m) and extracted with CH₂Cl₂ (3×25 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to afford the crude product **3**, that was purified by flash chromatography (cyclohexane-ethyl acetate).

References: R. Ballini, D. Fiorini, M. V. Gil, A. Palmieri, *Tetrahedron*, **60**, 2799 (2004).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Michael reaction, indole, iodine

**Experimental procedures:**

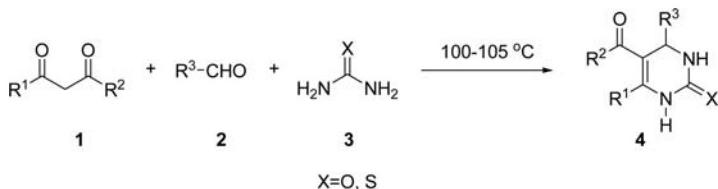
Iodine (5 mol%) was added to a mixture of indole (1 mmol) and ketone (1 mmol). After stirring for 30 min, the mixture was chromatographed over silica gel using ethyl acetate-hexane (10:90) to afford the pure product.

References: B. K. Banik, M. Fernandez, C. Alvarez, *Tetrahedron Lett.*, **46**, 2479 (2005).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: dihydropyrimidinone, Biginelli reaction

**Experimental procedures:**

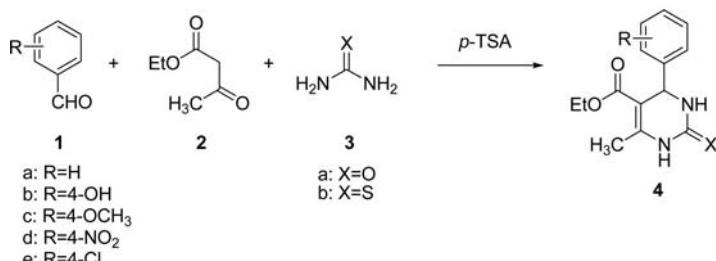
A mixture of benzaldehyde (530 g, 5 mol), ethyl acetoacetate (650 g, 5 mol), and urea (360 g, 6 mol) in a 2-L round-bottomed flask was stirred by a mechanical stirrer at room temperature for 2 min for uniform mixing, and then the temperature (oil bath) was raised to 100–105 °C. No exothermic reaction was observed during addition and mixing. Stirring was continued for another 1 h at that temperature. With the progress of reaction (during approximately the first 20 min all the urea dissolved, and solids started to appear) the reaction mixture became a thick slurry with the solids being deposited. At this stage, although no efficient stirring or agitation was possible, the reaction was not affected. After 1 h the reaction mixture was cooled in an ice-water bath (0–5 °C), and water (100 mL) followed by cold rectified spirit (50 mL) was added to provide a colorless solid (1.025 kg, 79%) which was practically pure, mp 201–202 °C (lit. 202–204 °C).

References: B. C. Ranu, A. Hajra, S. S. Dey, *Org. Process Res. Dev.*, **6**, 817 (2002).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Biginelli reaction, tetrahydropyrimidinone



Experimental procedures:

A mixture of an aromatic aldehyde (25 mmol), ethyl acetoacetate (25 mmol), urea (50 mmol), and *p*-TSA (200 mg) was ground for 2–3 min using a mortar and pestle of appropriate size. The initial syrupy reaction mixture solidified within 4–15 min. The solid was washed with cold water and recrystallized from ethanol.

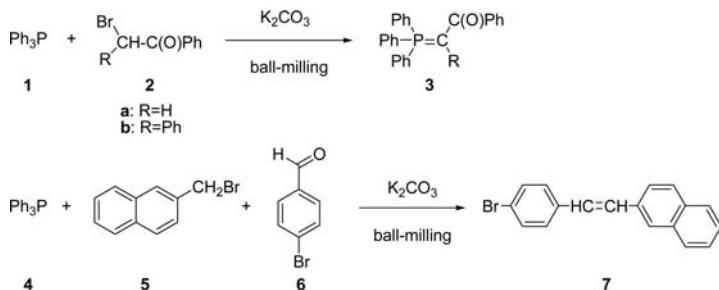
The large scale preparation of **4aa** was carried out by grinding benzaldehyde (1.06 kg, 10 mol), ethyl acetoacetate (1.30 kg, 10 mol), urea (1.20 kg, 20 mol) and *p*-TSA (80 g) for 3 min using kitchen Aid Mixture. The usual work-up of the reaction as stated above gave **4aa** with 93% yield.

References: A. K. Bose, S. Pednekar, S.N. Ganguly, G. Chakraborty, M.S. Manhas, *Tetrahedron Lett.*, **45**, 8351 (2004).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Wittig reaction, phosphorus ylide, ball-milling



Experimental procedures:

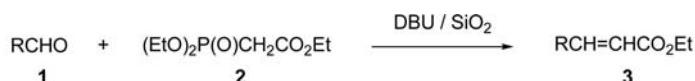
0.50 g (1.9 mmol) of triphenylphosphine, 0.42 g (1.9 mmol) of 2-bromomethyl-naphthalene, 0.36 g (2.0 mmol) of 4-bromobenzaldehyde and 0.50 g (3.6 mmol) of anhydrous K_2CO_3 were placed in a hardened-steel vial in a glove box under helium. The vial was sealed in helium atmosphere and the sample was ball-milled for 8 h. The powder formed was first analyzed by solid-state ^{31}P MAS NMR spectroscopy, then loaded on the top of a silica-gel filled chromatographic column, and the mixture of (*E*)- and (*Z*)-1-(4-bromophenyl)-2-(2-naphthyl)-ethylene (**7**) was isolated by elution with hexane and toluene (*E*:*Z* ratio ca. 3.5:1 by 1H NMR in $CDCl_3$) in 93% yield (0.54 g).

References: V.P. Balema, J.W. Wiench, M. Pruski, V.K. Pecharsky, *J. Am. Chem. Soc.*, **124**, 6244 (2002).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Horner-Wadsworth-Emmons reaction, DBU, triethylphosphonoacetate



R: Ph, *p*-CH₃O, *p*-CH₃, 4-Cl, 4-CN, 4-NO₂, PhCH₂CH₂, *c*-C₆H₁₁, *n*-C₇H₁₅, (CH₃)₃C

Experimental procedures:

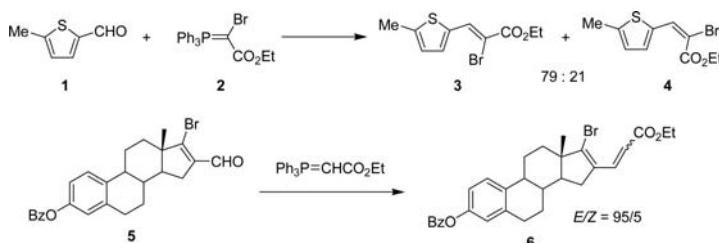
A mixture of DBU (1.53 g, 10 mmol, 98%) in dry silica gel (4 g) was added to a mixture of benzaldehyde (1.06 g, 10 mmol, 97%) and triethylphosphonoacetate (2.25 g, 10 mmol, 98%) in silica gel (DavisilTM-646, 6 g). The mixture was then stirred for 4 h at room temperature. The reaction mixture was placed in a short column and eluted with diethyl ether (60 mL). Concentration of the eluent afforded the crude product (1.65 g, 94%) with >97% purity as a mixture of isomers (*E/Z*=98/2).

References: Y.Z. Jin, N. Yasuda, J. Inanaga, *Green Chem.*, **4**, 498 (2002).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Wittig reaction, olefination



Experimental procedures:

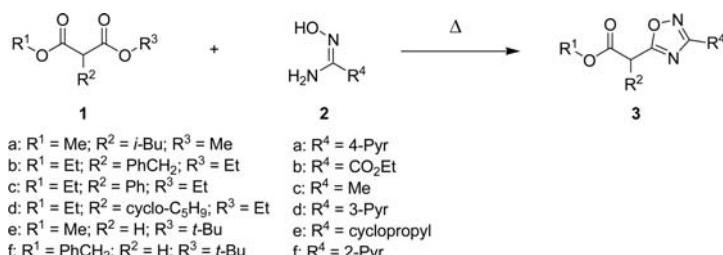
To 5-methylthienyl-2-carbaldehyde (**1**; 874 mg, 6.9 mmol) was added within 5 min solid ethyl (triphenylphosphoranylidene)bromoacetate (**2**; 4.16 g, 9.7 mmol). The mixture evolved heat and formed a melt. The flask was covered and was warmed to 100 °C for 10 min (oil bath, sand bath or electric oven). After cooling the mixture the melt was transferred and subjected to column chromatography on silica gel (ether-hexane, 1:5) to give ethyl 2-bromo-3-(*E*)-(5'-methyl-thien-2'-yl)acrylate (**3**; 1.48 g, 79%) and ethyl 2-bromo-3-(*Z*)-(5'-methyl-thien-2'-yl)acrylate (**4**; 394 mg, 21%) as a colorless oil.

References: T. Thiemann, M. Watanabe, Y. Tanaka, S. Mataka, *New J. Chem.*, **28**, 578 (2004).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: *a*-1,2,4-oxadiazolo ester, amidoxime, malonic diester



Experimental procedures:

Amidoxime **2d** (140 mg, 1 mmol) and *tert*-butyl methyl malonate **1e** (348 mg, 2 mmol) were mixed in a test tube with a stir bar. The test tube was then placed

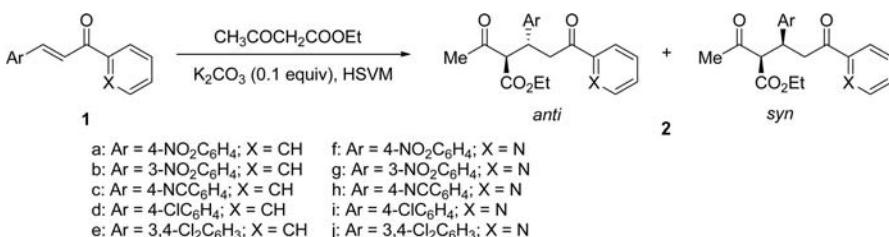
in an oil bath and heated to 120 °C for 2 h with stirring. After the reaction was completed, the reaction mixture was applied to a silica gel column. Flash chromatography yielded compound **3ed** as a white solid (156 mg) in 71% yield.

References: W. Du, W.K. Hagmann, J.J. Hale, *Tetrahedron Lett.*, **47**, 4271 (2006).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Michael reaction, azachalcone, high-speed vibration milling



Experimental procedures:

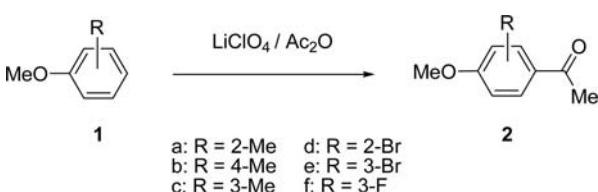
A mixture of an unsaturated ketone, ethyl acetoacetate and K_2CO_3 in a molar ratio of 1:1:0.1 was introduced, together with a stainless-steel ball of 6.0 mm diameter, into a stainless-steel capsule ($9.0 \times 26.0 \text{ mm}^2$). The reaction capsule was fixed on the vibration arm of a home-built ball-milling apparatus, and was vibrated vigorously at a rate of 3500 rpm at room temperature. The resulting powder was collected and washed with 10 mL of water to remove K_2CO_3 completely and then dried to afford the desired product **2**.

References: Z. Zhang, Y.-W. Dong, G.-W. Wang, K. Komatsu, *Chem. Lett.*, **33**, 168 (2004).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Friedel-Crafts acylation, acetyl anhydride



Experimental procedures:

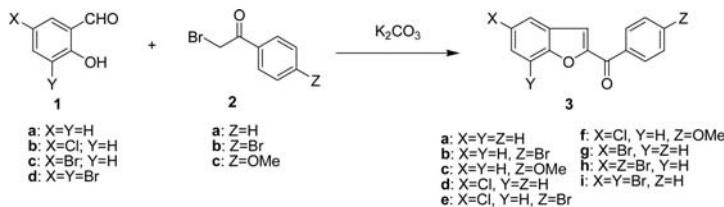
2 equiv. of commercial anhydrous LiClO₄ were dried *in vacuo* (0.1 Torr) at 140 °C for 2 h. After cooling, the anhydride (1.05 equiv.) was added to LiClO₄ and the mixture was heated at the desired temperature until LiClO₄ was dissolved. Then the substrate (1 equiv.) was added dropwise and the reaction was monitored by GLC. After the reaction was complete, the mixture was cooled and CH₂Cl₂ was added. The precipitated LiClO₄ was recovered by centrifugation and reutilized. The organic layer was treated with aqueous NaHCO₃ and dried over MgSO₄. The reaction product was recovered by simple removal of the solvent and purified by column chromatography when necessary.

References: G. Bartoli, M. Bosco, E. Marcantoni, M. Massaccesi, S. Rinaldi, L. Sambri, *Tetrahedron Lett.*, **43**, 6331 (2002).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Rap-Stoermer reaction, salicylaldehyde, phenacyl bromide

**Experimental procedures:**

A mixture of **1a** (0.61 g, 5 mmol), **2a** (0.99 g, 5 mmol) and K₂CO₃ (1.38 g, 10 mmol) was heated at 80 °C for 1 h, the reaction mixture was then washed with water to give **3a** in 98% yield (1.09 g).

References: K. Yoshizawa, S. Toyota, F. Toda, I. Csöregi, *Green Chem.*, **5**, 353 (2003).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Friedel-Crafts acylation, ZnO

**Experimental procedures:**

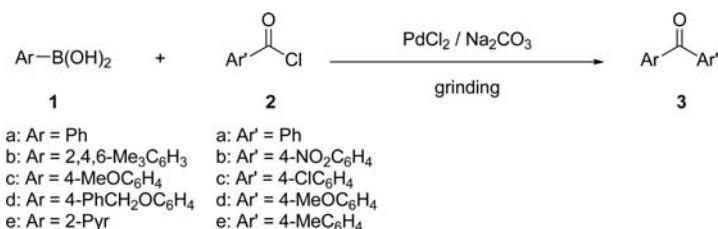
An aromatic compound (1 mmol) was added to a mixture of ZnO (powder, 0.04 g, 0.5 mmol) and acid chloride (1 mmol) at room temperature and stirred with a magnetic stirrer. Color (usually pink, but in a few cases green or blue) developed immediately and darkened with the progress of the reaction. The reaction mixture was kept at room temperature with occasional stirring for a certain period of time as required to complete the reaction (monitored by TLC). The solid mass was then eluted with dichloromethane (20 mL), and the dichloromethane extract was then washed with an aqueous solution of sodium sulfate. Evaporation of solvent furnished the practically pure product.

References: M. H. Sarvari, H. Sharghi, *J. Org. Chem.*, **69**, 6953 (2004).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Suzuki coupling, acyl chloride, boronic acid

**Experimental procedures:**

To a mixture of benzeneboronic acid (122 mg, 1 mmol), sodium carbonate (212 mg, 2 mmol) and 4-methoxybenzoyl chloride (0.174 mL, 1.5 mmol) in a mortar, palladium chloride (6 mg, 3.3 mol%) was added with continuous grinding with a pestle at 25–30 °C. The reaction was monitored by TLC. After completion of the reaction, ether (10 mL) was added and the mixture was washed with so-

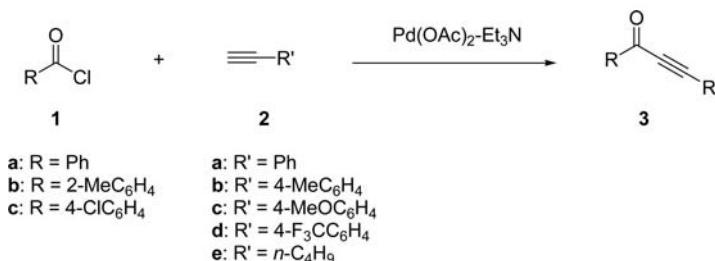
dium bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated and further purified by column chromatography (petroleum ether/ethyl acetate = 9 : 1).

References: B.P. Bandgar, A.V. Patil, *Tetrahedron Lett.*, **46**, 7627 (2005).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: alkyne, palladium (II) acetate, ynone



Experimental procedures:

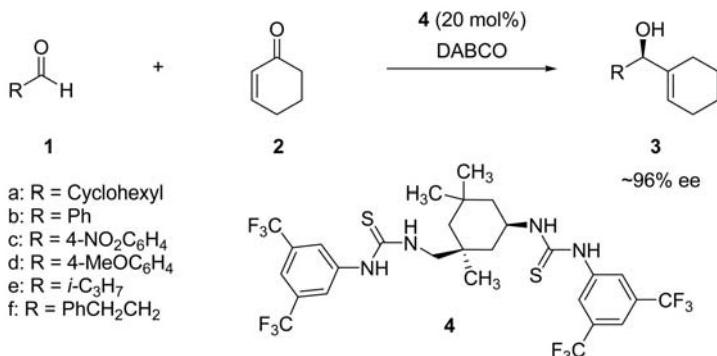
A mixture of acid chloride (1 mmol), terminal alkyne (1 mmol), Et₃N (1 mmol) and Pd(OAc)₂ (0.2 mol%) was stirred at room temperature for 10 min under an atmosphere of argon. Completion of the reaction was monitored by TLC. After completion, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water to dissolve the amine hydrochloride formed. The organic layer was then separated, dried over magnesium sulfate, filtered and concentrated under vacuum to obtain the crude product. The crude product was further purified by column chromatography using ethyl acetate/petroleum ether as eluent to afford the desired product.

References: S.S. Palimkar, P.H. Kumar, N.R. Jogdand, T. Daniel, R.J. Lahoti, K.V. Srivivasan, *Tetrahedron Lett.*, **47**, 5527 (2006).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Morita-Baylis-Hillman reaction, cyclohexanecarbaldehyde

**Experimental procedures:**

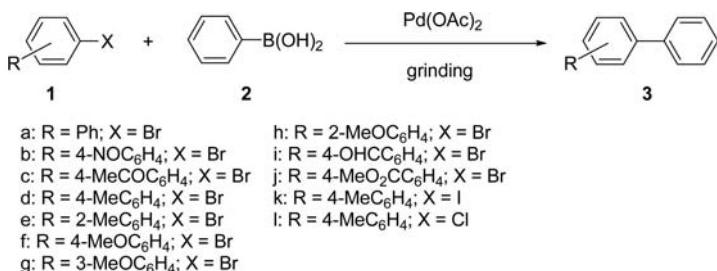
DABCO (5.61 mg, 50.0 mol) and catalyst **4** (35.6 mg, 50.0 mol) were dissolved in 2-cyclohexen-1-one **2** (96.5 L, 96.1 mg, 1.00 mmol), and tridecane (15.2 L, 11.5 mg, 62.5 mol) was added as internal standard. The mixture was cooled to 10°C on a coolable shaker plate and cyclohexanecarbaldehyde **1a** (30.1 L, 28.0 mg, 250 mol) was added. The mixture was shaken for 72 h at 10°C and 400 rpm. Aliquots of 10.0 L were taken at intervals and analyzed by GC on a chiral stationary phase. In the case of HPLC analysis, the reaction was stopped after 72 h and the product isolated by column chromatography (*n*-hexane: ethyl acetate 3 : 1).

References: A. Berkessel, K. Roland, J.M. Neudörfl, *Org. Lett.*, **8**, 4195 (2006).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Suzuki coupling, boronic acid

**Experimental procedures:**

A grinding jar was loaded with aryl bromide (1 mmol), phenylboronic acid (122 mg, 1 mmol), Pd(OAc)₂ (10 mg, 0.045 mmol, 4.5 mol%) and triethylamine

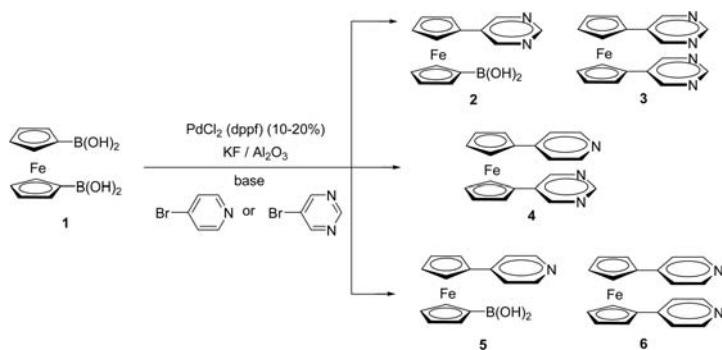
(300 mg, 0.41 mL, 3 mmol). NaCl was added slowly to the reaction mixture with agitation with a spatula until a damp paste was formed. The consistency of the paste was such that no liquid remained in the grinding jar but the granules of NaCl clung to the spatula when lifted from the mixture, this taking roughly 2 g NaCl. A grinding ball was then added, the jar closed and placed in the mixer mill and the reaction mixture ground for 10 min. After grinding, the jar was then opened cautiously to avoid loss of material attached to the lid. All the material inside the jar was scraped into a conical flask and the jar rinsed with water and then ether and the washings placed with the scrapings. Water (30 mL) and ether (30 mL) were added to the flask and the entire contents transferred to a separating funnel. HCl (40 mL, 2 M) was added and, after agitation, the organic layer was separated, dried over anhydrous MgSO₄, filtered and concentrated by rotary evaporation. The products were purified by recrystallization, or flash chromatography on silica gel using hexane or hexane/ethyl acetate as eluent.

References: L.M. Klingensmith, N.E. Leadbeater, *Tetrahedron Lett.*, **44**, 765 (2003).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: pyridine ferrocenyl complex, Suzuki coupling



Experimental procedures:

To a mixture of KF/Al₂O₃ (0.725 g, 40 wt%) and PdCl₂[1,1'-bis(diphenylphosphino)ferrocene] (0.1 equiv., 0.05 mmol, 40.8 mg) was added ferrocene-1,1'-diboronic acid [Fe(5-C₅H₄-B(OH)₂)₂] **1** (1 equiv., 0.5 mmol, 137 mg). The solid mixture was ground at room temperature in the open air until homogeneous; 4-bromopyridium hydrochloride (1.3 equiv., 0.65 mmol, 126.1 mg) was then added with grinding. The mixture was ground at room temperature for an additional 10–15 min to ensure efficient mixing. KOH (1.3 equiv., 0.65 mmol, 36.4 mg) was added to accelerate the reaction. To make the mixture more homogeneous, 0.1–0.2 mL of methanol was added and the slurry ground at room temperature for an

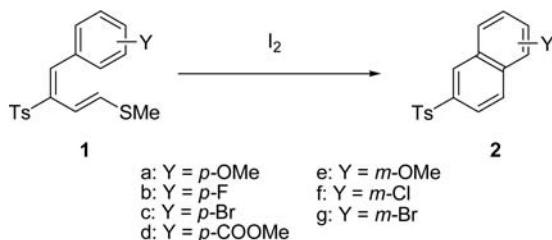
additional 10 min, then evaporated under reduced pressure. The reaction was followed by TLC. The mixture was purified by silica gel flash column chromatography ($\text{CH}_2\text{Cl}_2:\text{MeOH}=95:5$) yielding 0.0875 g of pure product as a red solid **2** (yield 57%).

References: D. Braga, D. D'Addario, M. Polito, *Organometallics*, **23**, 2810 (2004).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: iodine, (*p*-tolylsulfonyl)naphthalene



Experimental procedures:

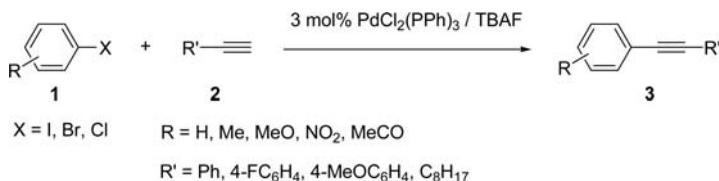
To a 30-mL round-bottom flask capped with a septum were added 0.5 mmol of the substrate (**1**) and the desired amount of iodine molecule. The mixture was mechanically mixed for 10 min. After standing at room temperature, the mixture was dissolved in ethyl acetate (20 mL) and washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL \times 2). After the organic layer was dried over MgSO_4 and concentrated *in vacuo*, the residue was purified by recrystallization or silica-gel column chromatography to give the corresponding naphthalene derivative (**2**).

References: S. Matsumoto, K. Kumazawa, K. Ogura, *Bull. Chem. Soc. Jpn.*, **76**, 2179 (2003).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Sonogashira cross-coupling, alkyne



Experimental procedures:

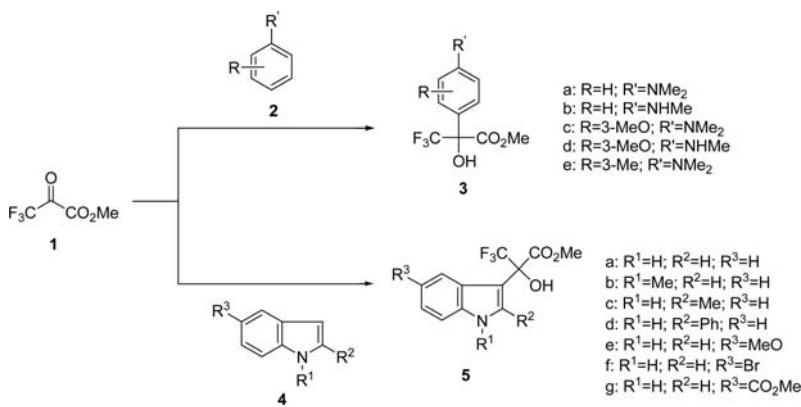
A mixture of aryl halide **1** (0.5 mmol), alkyne **2** (0.6 mmol), PdCl₂(PPh₃)₂ (3 mol%), and TBAF·3H₂O (3 equiv.) was stirred under N₂ at 80 °C for the desired time until complete consumption of starting material, as monitored by TLC. After the mixture was washed with water, extracted with ether, and evaporated, the residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the corresponding coupled products **3**.

References: Y. Liang, Y.-X. Xie, J.-H. Li, *J. Org. Chem.*, **71**, 379 (2006).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Friedel-Crafts alkylation, methyl trifluoropyruvate



Experimental procedures:

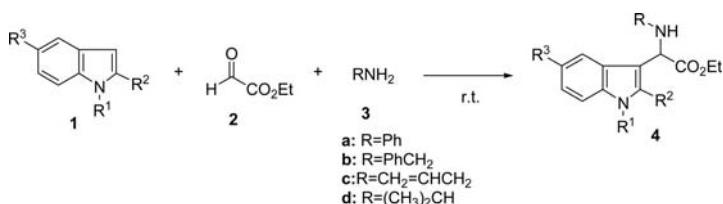
To indole (**4a**, 0.3 mmol) in a test tube was added dropwise methyl trifluoropyruvate (**1**, 0.3 mmol) at ambient temperature. The reaction was stirred for 1 min. The crude product was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1 : 4) to give a light red solid **5a** (96%).

References: J.-L. Zhao, L. Liu, H.-B. Zhang, Y.-C. Wu, D. Wang, Y.J. Chen, *Tetrahedron Lett.*, **47**, 2511 (2006).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: indole, glyoxylate, Friedel-Crafts alkylation



Experimental procedures:

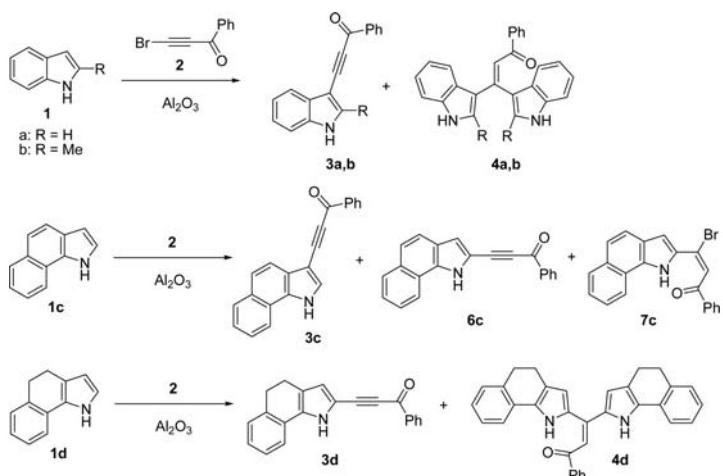
To a stirred mixture of indole (35 mg, 0.3 mmol) and aniline (42 μL, 0.45 mmol) ethyl glyoxylate (freshly distilled; 50 mg, 0.45 mmol) was added at ambient temperature. The reaction mixture was stirred for 1 min. The crude product was purified by flash chromatography on silica gel (petroleum ether-EtOAc, 4:1) to give ethyl 2-(1*H*-indol-3-yl)-2-(phenylamino)acetate as a colorless oil (66 mg, 75%) and ethyl 2-(1*H*-indol-3-yl)-2-hydroxyacetate (12 mg, 19%).

References: J.-L. Zhao, L. Liu, H.-B. Zhang, Y.-C. Wu, D. Wang, Y.-J. Chen, *Synlett*, 96 (2006).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: indole, 1-benzoyl-2-bromoacetylene, 3-(2-benzoylethynyl)indole



Experimental procedures:

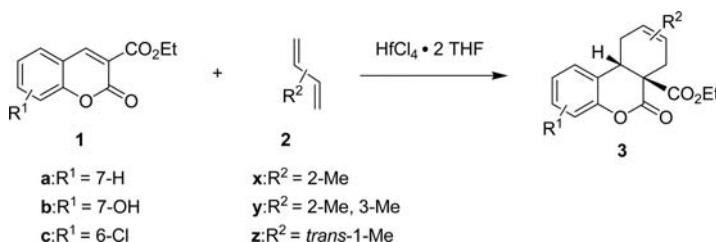
Equimolar amounts of indoles **1a–c** or pyrrole **1d** (0.5–1.0 mmol) and 1-benzoyl-2-bromoacetylene **2** were ground together at room temperature with a 10-fold excess (by weight) of Al₂O₃ (chromatography grade, Merck, pH 6.8–7.8) in a china mortar for 1–2 min. The reaction mixture self-heated (5–8 °C) and within 10 min turned from yellow to orange-brown. After 60 min, the reaction products were extracted sequentially with n-hexane (10–15 mL), n-hexane-Et₂O (2:1–1:2) (40–50 mL) and Et₂O (15–20 mL). The fractions were further chromatographed on a column or by thin layer (Al₂O₃) to yield indoles **3a–c**, **6c** or pyrrole **3d** as yellow-orange or red crystals (after recrystallization from benzene) and 1,1-di(indolyl)-2-benzoylethenes **4b, d**.

References: B.A. Trofimov, Z.V. Stepanova, L.N. Sobenina, A.I. Mikhaleva, I.A. Ushakov, *Tetrahedron Lett.*, **45**, 6513 (2004); L.N. Sobenina, A.P. Demenev, A.I. Mikhaleva, I.A. Ushakov, A.M. Vasiltsov, A.V. Ivanov, B.A. Trofimov, *Tetrahedron Lett.*, **47**, 7139 (2006).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Diels-Alder reaction, hafnium chloride, 3-ethoxycarbonylcoumarin

**Experimental procedures:**

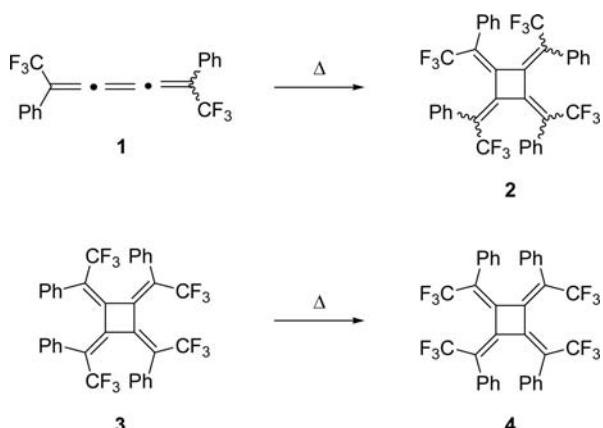
A screw-capped vial equipped with a magnetic stirrer was charged with HfCl₄·2 THF (0.05 mmol, 0.023 g) and 3-ethoxycarbonylcoumarin (**1a**; 1.0 mmol, 0.218 g), then isoprene (**2x**; 4.0 mmol, 0.272 g) was added. The resulting mixture was left under magnetic stirring at 30 °C for 6 h. After silica-gel column chromatography of the final mixture (EtOAc/petroleum ether, 2/8 gradient) cycloadduct **3ax** was isolated; yield: 0.272 g (95%).

References: F. Fringuelli, R. Girotti, F. Pizzo, E. Zunino, L. Vaccaro, *Adv. Synth. Catal.*, **348**, 297 (2006).

Type of reaction: C=C bond formation

Reaction condition: solid-state

Keywords: [2+2]cycloaddition, cumulene



Experimental procedures:

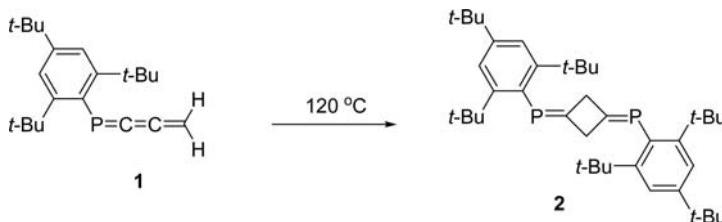
The cumulene **1** (340 mg, 1 mmol) was placed in a flask which was then purged with argon. The flask was put in a preheated glass-tube oven at 150 °C. After 24 h, the gummy solid was subjected to NMR analysis and then chromatographed on silica gel (3–5% EtOAc/hexane) to give 251 mg (74%) of radialene isomers **2**, as well as the recovered **1** (19 mg, 6%). Isomerization of **3** (40 mg) was performed similarly to the dimerization described above. After 70 h, the remaining solid was subjected to NMR analysis and then recrystallized from hexane (1 mL) to give 25 mg (63%) of pure isomer **4**.

References: H. Uno, K. Kasahara, N. Nibu, S. Nagaoka, N. Ono, *J. Org. Chem.*, **65**, 1615 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: [2+2]cycloaddition, 1-phosphaallene

**Experimental procedures:**

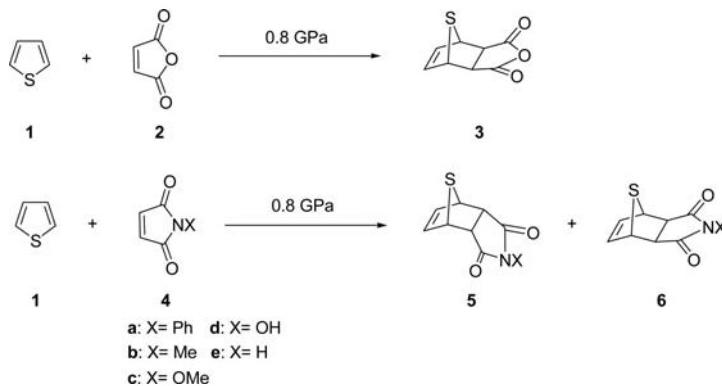
Single crystals of **1** (50 mg, 1.7 mmol; crystallized from EtOH) were heated at 120 °C in a 5-mm capillary tube for 24 h. The residual yellow crystals were dissolved in [D]chloroform, and peaks in a 31 P NMR spectrum corresponding to **1** and **2** were observed in a 1:3 ratio.

References: S. Ito, S. Sekiguchi, M. Yoshifuji, *Eur. J. Org. Chem.*, 4838 (2003).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Diels-Alder reaction, thiophene, high pressure

**Experimental procedures:**

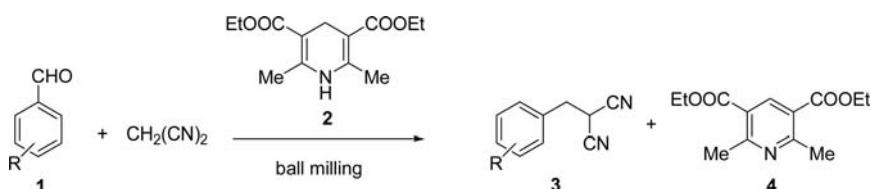
A mixture of thiophene (1.495 g, 17.8 mmol) and maleic anhydride (441 mg, 4.5 mmol) was placed in a Teflon reaction vessel (volume: 3.9 ml), and the mixture was treated at 0.8 GPa and 100 °C for 2 days. After cooling the reaction mixture and releasing the pressure, the excess of thiophene was evaporated and the crude solid product (785 mg) was purified by column chromatography on silica gel (hexane/AcOEt=1:1) to give the exo adduct **3** (761 mg, 93%) as a colorless solid.

References: K. Kumamoto, I. Fukuda, H. Kotsuki, *Angew. Chem. Int. Ed.*, **43**, 2015 (2004).

Type of reaction: C=C bond formation

Reaction condition: solvent-free

Keywords: reductive benzylization, malononitrile, 4-methylaniline



R = 4-Cl, 4-Br, 4-NO₂, 4-CN, 3-NO₂, 2-NO₂, 3,4-Cl, 2,4-Cl, H, 4-N(Me)₂

Experimental procedures:

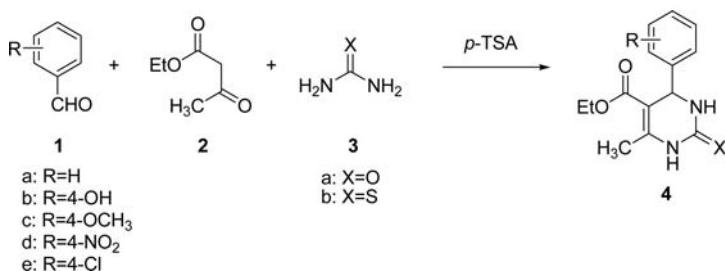
A mixture of aldehyde **1** (0.5 mmol), malononitrile (0.5 mmol) and Hantzsch 1,4-dihydropyridine **2** (0.51 mmol) was introduced, together with a stainless ball of 7.0 mm diameter, into a stainless steel jar (5 mL). The same mixture vessels were also introduced into a second, parallel jar. The two reaction vessels were closed and fixed on the vibration arms of a ball-milling apparatus (Retsch MM200 mixer mill, Retsch GmbH, Haan, Germany) and vibrated vigorously at a rate of 1800 rpm (30 Hz) at room temperature for 90 min.

References: Z. Zhang, J. Gao, J.-J. Xia, G.-W. Wang, *Org. Biomol. Chem.*, **3**, 1617 (2005).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Biginelli reaction, tetrahydropyrimidinone



Experimental procedures:

A mixture of an aromatic aldehyde (25 mmol), ethyl acetoacetate (25 mmol), urea (50 mmol), and *p*-TSA (200 mg) was ground for 2–3 min using a mortar and pestle of appropriate size. The initial syrupy reaction mixture solidified within 4–15 min. The solid was washed with cold water and recrystallized from ethanol.

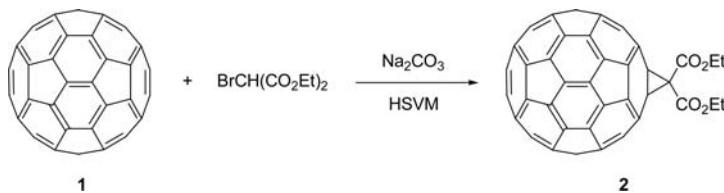
The large scale preparation of **4aa** was carried out by grinding benzaldehyde (1.06 kg, 10 mol), ethyl acetoacetate (1.30 kg, 10 mol), urea (1.20 kg, 20 mol) and *p*-TSA (80 g) for 3 min using kitchen Aid Mixture. The usual work-up of the reaction as described above gave **4aa** with 93% yield.

References: A. K. Bose, S. Pednekar, S. N. Ganguly, G. Chakraborty, M. S. Manhas, *Tetrahedron Lett.*, **45**, 8351 (2004).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: C₆₀, high-speed vibration milling, Bingel reaction



Experimental procedures:

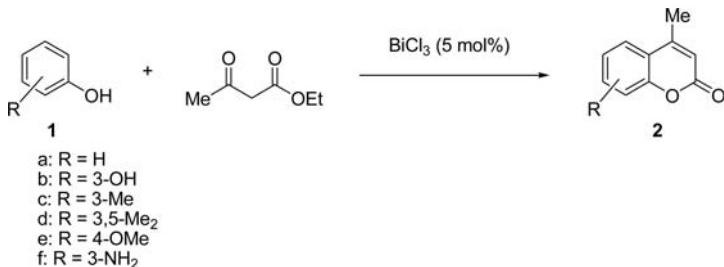
When a mixture of C₆₀ (28.8 mg), ethyl bromomalonate and Na₂CO₃ in 1:1:1 molar ratio was vigorously milled for 30 min, monoadduct **2** was obtained in 51% (81% based on consumed C₆₀) yield together with 7% (12% based on consumed C₆₀) of bisadducts.

References: G.-W. Wang, T.-H. Zhang, Y.-J. Li, P. Lu, H. Zhan, Y.-C. Liu, Y. Murata, K. Komatsu, *Tetrahedron Lett.*, **44**, 4407 (2003).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Pechmann reaction, bismuth (III) chloride, coumarin



Experimental procedures:

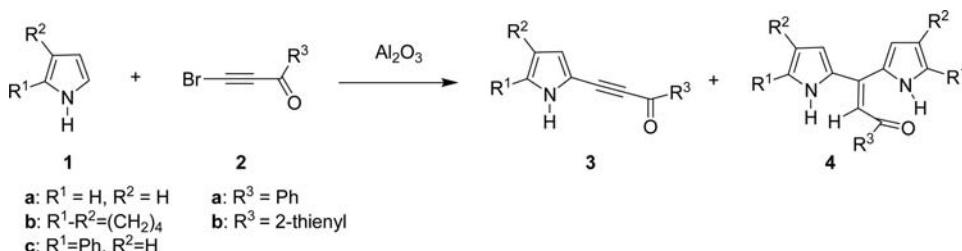
A mixture of resorcinol (550 mg, 5 mmol) and ethyl acetoacetate (650 mg, 5 mmol) was heated at 75 °C for 1 h (TLC). The reaction mixture was cooled to room temperature and poured into crushed ice (10 g). The crystalline products were collected by filtration under suction and washed with cold H₂O. The pure product was obtained by recrystallization from hot EtOH; mp 184–186 °C.

References: S. K. De, R. A. Gibbs, *Synthesis*, **8**, 1231 (2005).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Sonogashira coupling, ethynylation, pyrrole

**Experimental procedures:**

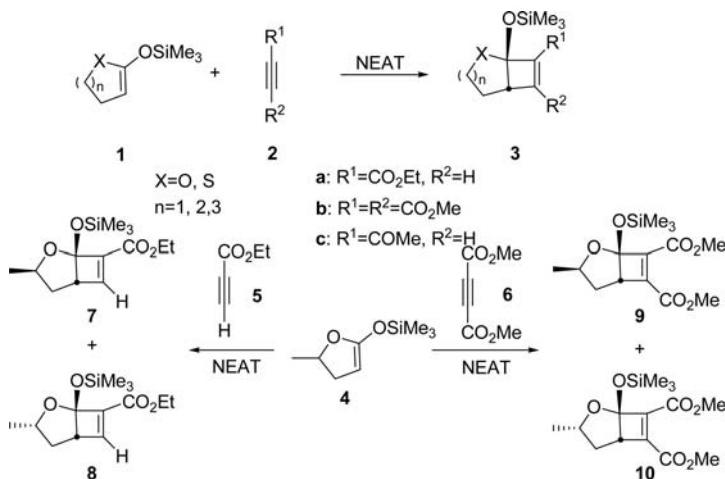
Equimolar amounts (0.5–1.0 mmol) of pyrrole **1** and a 1-acyl-2-bromoacetylene **2** were ground together at room temperature with a 10-fold excess (by weight) of Al₂O₃ (chromatography grade, washed with distilled water and ethanol and dried until constant weight) in a china mortar and pestle for 1–2 min. The reaction mixture self-heated (5–8 °C) and within 10 min turned from yellow to orange-brown. After 30–60 min, the reaction products were extracted sequentially with n-hexane (10–15 mL), n-hexane–Et₂O (2:1–1:2) (40–50 mL) and Et₂O (15–20 mL). The fractions were further chromatographed on a column or in thin layer (Al₂O₃) to yield pyrroles **3** as air-stable yellow-orange needles (after recrystallization from n-hexane–Et₂O, 1:1), and 1,1-di(pyrrol-2-yl)-2-acylethenes **4**.

References: B. A. Trofimov, Z. V. Stepanova, L. N. Sobenina, A. I. Mikhaleva, I. A. Ushakov, *Tetrahedron Lett.*, **45**, 6513 (2004).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: [2+2]cycloaddition, cyclobutene, β -oxocyclobutanecarboxylate



Experimental procedures:

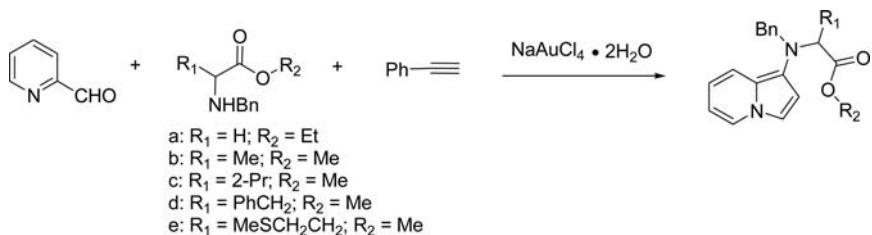
To the ketene silyl acetal (1 equiv.) was added, at room temperature, neat ethyl propynoate, dimethyl acetylenedicarboxylate (DMAD) or ethynyl methyl ketone (1 equiv.). The mixture was stirred for 5 h at room temperature *in vacuo* (0.1 Torr) for 30 min. Purification of the crude reaction mixture by silica gel column chromatography (ethyl acetate/hexane, 5:95) afforded the cycloadducts.

References: M. Miesch, F. Wendling, *Eur. J. Org. Chem.*, 3381 (2000).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: pyridine-2-carboxylate, amino acid, alkyne



Experimental procedures:

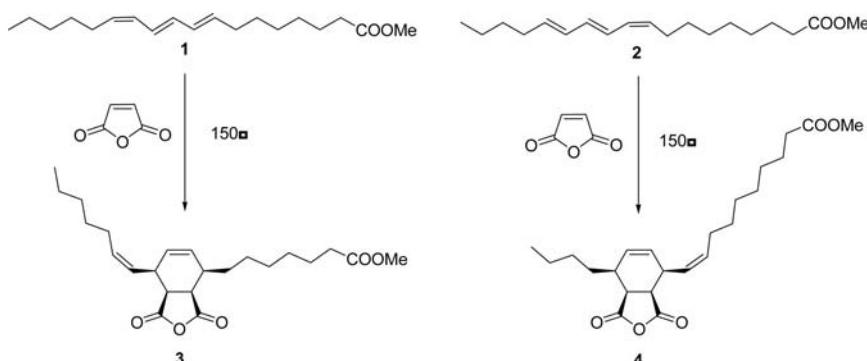
Pyridine-2-carboxaldehyde (95 L, 1 mmol), alkyne (1.2 mmol), $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$ (4 mg, 0.01 mmol) and amine (1.1 mmol) were added successively to a Schlenk tube at room temperature. The resulting mixture was stirred at 60 °C until the reaction was completed, as monitored by thin-layer chromatography. The crude product was purified by flash chromatography on silica gel affording the indolizine products.

References: B. Yan, Y. Liu, *Org. Lett.*, **9**, 4323 (2007).

Type of reaction: C=C bond formation

Reaction condition: solvent-free

Keywords: Diels-Alder addition, maleic anhydride, methyl α -olenostearate



Experimental procedures:

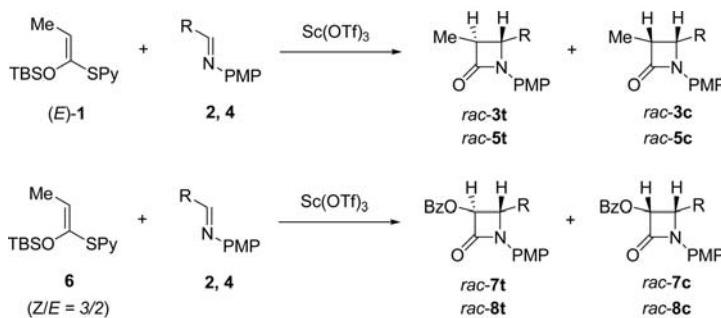
A mixture of calendic acid methyl ester **1** (3 mmol, 1.50 g) and maleic anhydride (5 mmol, 0.49 g) was heated for 2 h at 150 °C under nitrogen. The reaction was followed by thin-layer chromatography [petroleum ether–diethyl ether (7:3), R_f **1**=0.60, R_f **3**=0.23]. Purification of product **3** was achieved by column chromatography [silica gel using petroleum ether/diethyl ether (7:3) and petroleum ether/ethyl acetate (1:1) as eluent]. Fractions containing product **3** were collected and the solvent was removed *in vacuo*. Compound **3** was recrystallized from petroleum ether/diethyl ether (4:1).

References: U. Biermann, W. Butte, T. Eren, D. Haase, J.O. Metzger, *Eur. J. Org. Chem.*, 3859 (2007).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: β -lactam, silyl ketene thioacetal, imine, scandium triflate



2, 3, 7: R = COOEt; 4, 5, 8: R = Ph

Py = 2-pyridyl; TBS = *t*-BuMe₂Si; PMP = 4-MeOPh

Experimental procedures:

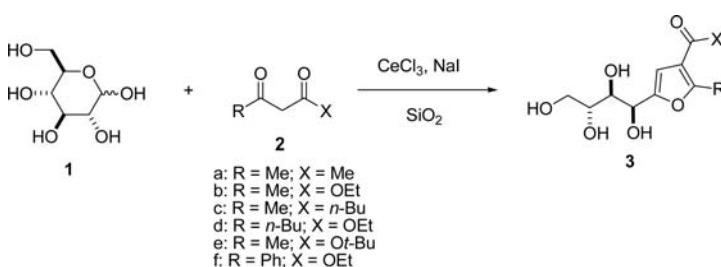
Sc(OTf)₃ (0.015 g, 0.03 mmol), imine **2** (0.062 g, 0.3 mmol), and silyl ketene thioacetal **1** (0.169 g, 0.6 mmol) were added in this order to a 2-mL glass vial and the resulting dark mixture was stirred for 20 h at room temperature. Dichloromethane (0.25 mL) was then added and the resulting suspension was purified by flash chromatography with a 10:90 AcOEt/hexane mixture as eluent. The trans-product **3t** (0.028 g, 35.5% yield) was eluted first as a thick pale yellow oil followed by the cis-product **3c** (0.028 g, 35.5% yield) which was also a thick pale yellow oil.

References: M. Benaglia, F. Cozzi, A. Puglisi, *Eur. J. Org. Chem.*, 2865 (2007).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: Garcia Gonzalez reaction, aldohexose, β -dicarbonyl compound



Experimental procedures:

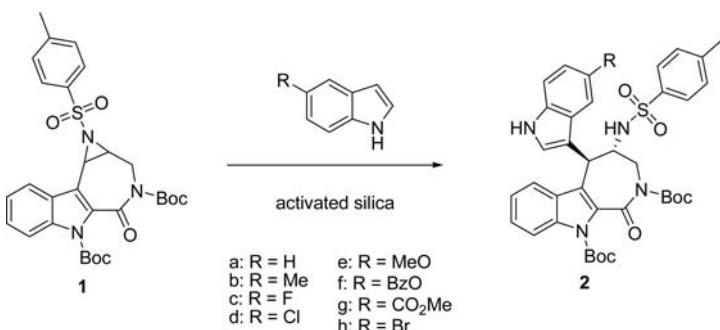
Silica gel (0.5 g) was added to a mixture of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (0.113 g, 0.3 mmol) and NaI (13.4 mg, 0.3 mmol) in acetonitrile (7 mL), and the mixture was stirred overnight at room temperature. D-Glucose **1** (0.18 g, 1.0 mmol) was added, and the reaction mixture was then stirred at room temperature for 1 h. The acetonitrile was removed by rotary evaporation and to the resulting powder was added 2,4-pentanedione **2a** (0.17 mL, 1.3 mmol). The mixture was then mechanically stirred at an external temperature of 50 °C until the disappearance of the starting aldohexose (22 h, checked by TLC analysis). After addition of methanol (15 mL), the mixture was passed through a short pad of Celite and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography on a silica gel column (eluent, dichloromethane-ethyl acetate, 90:10) to give 0.26 g (95% yield) of the corresponding Garcia Gonzalez adduct **3**.

References: G. Bartoli, J.G. Fernandez-Bolanos, G. Di Antonio, G. Foglia, S. Giulia, R. Gunnella, M. Mancinelli, E. Marcantonio, M. Paoletti, *J. Org. Chem.*, **72**, 6029 (2007).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: indole aziridine, *N*-arylsulfonylaziridine

**Experimental procedures:**

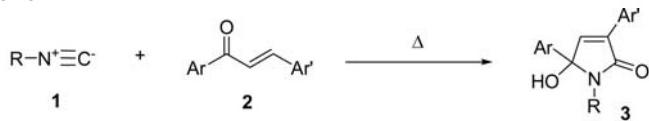
Aziridine (\pm)-**1a–c** (0.2 mmol) and an indole derivative (2 mmol) were dissolved in an appropriate solvent (e.g. CH_2Cl_2 , acetone or ethyl acetate) and activated silica (429 mg, 0.040–0.063 mmol) was added. The solvent was removed under reduced pressure and the solid mixture was heated under argon at 70 °C overnight (~12–16 h). Purification by column chromatography (silica gel 70–230 mesh, CH_2Cl_2 to $\text{CH}_2\text{Cl}_2:\text{MeOH}$ 10:1 as the gradient eluent) yielded the crude product.

References: H.M. Kaiser, I. Zenz, W.F. Lo, A. Spannenberg, K. Schroder, H. Jiao, D. Gordes, M. Beller, M.K. Tse, *J. Org. Chem.*, **72**, 8847 (2007).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: isocyanide, chalcone, 5-hydroxy-3,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-one.



- $a: R = \text{cyclohexyl}; Ar = \text{Ph}; Ar' = 4\text{-MeC}_6\text{H}_4$
 $b: R = \text{cyclohexyl}; Ar = \text{Ph}; Ar' = \text{Ph}$
 $c: R = \text{cyclohexyl}; Ar = \text{Ph}; Ar' = 4\text{-MeOC}_6\text{H}_4$
 $d: R = \text{cyclohexyl}; Ar = \text{Ph}; Ar' = 4\text{-ClC}_6\text{H}_4$
 $e: R = \text{cyclohexyl}; Ar = \text{Ph}; Ar' = 4\text{-FC}_6\text{H}_4$
 $f: R = \text{cyclohexyl}; Ar = \text{Ph}; Ar' = 3\text{-MeC}_6\text{H}_4$
 $g: R = \text{cyclohexyl}; Ar = 4\text{-MeC}_6\text{H}_4; Ar' = 4\text{-MeC}_6\text{H}_4$
 $h: R = \text{cyclohexyl}; Ar = 4\text{-MeC}_6\text{H}_4; Ar' = 4\text{-ClC}_6\text{H}_4$
 $i: R = \text{cyclohexyl}; Ar = 4\text{-MeC}_6\text{H}_4; Ar' = 4\text{-FC}_6\text{H}_4$
 $j: R = t\text{-BuCH}_2; Ar = \text{Ph}; Ar' = \text{Ph}$
 $k: R = t\text{-BuCH}_2; Ar = \text{Ph}; Ar' = 3\text{-MeC}_6\text{H}_4$
 $l: R = t\text{-BuCH}_2; Ar = \text{Ph}; Ar' = 4\text{-MeC}_6\text{H}_4$

Experimental procedures:

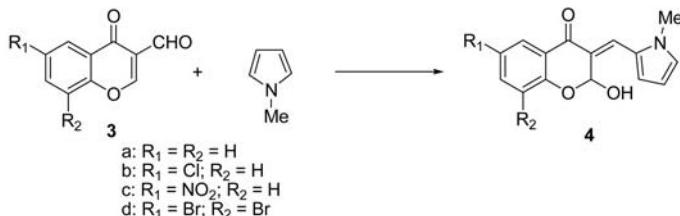
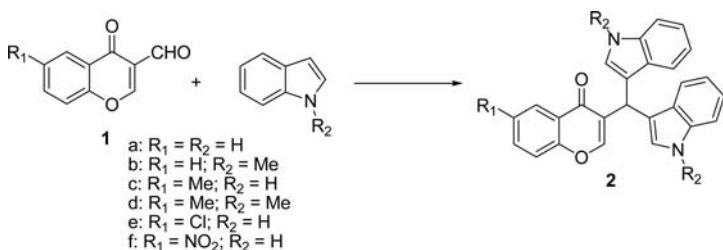
A mixture of 3-(4-methylphenyl)-1-phenyl-2-propen-1-one (0.444 g, 2 mmol) and cyclohexyl isocyanide (0.218 g, 2 mmol) was stirred at 150°C for 30 min. The reaction mixture was then cooled to room temperature and the residue was purified by column chromatography using 1:2 n-hexane-EtOAc as eluent. The solvent was removed and the solid residue was recrystallized from 1:1 n-hexane-EtOAc to afford **3a** as colorless crystals, mp 160–162°C, yield 0.64 g, 92%.

References: M. Adib, M. Mahdavi, M. Alizadeh, A. Noghani, H. Reza, R. Bijanzadeh, *Tetrahedron Lett.*, **48**, 8056 (2007).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: indole, *N*-methylpyrrole, 3-formylchromone



Experimental procedures:

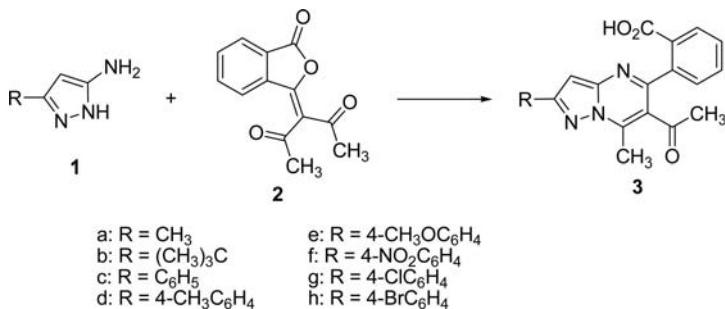
A solution of 3-formylchromone **1** (2.5 mmol) in an excess of indole or *N*-methyl-lindole (7.5 mmol) was heated at 85–90 °C for 5 h. Completion of the reaction was determined by the appearance of the solid reaction mixture. The precipitate, obtained from the hot solution, was twice recrystallized from n-butanol/*p*-xylene (4:1), washed with ethanol, and dried at 90 °C for 1 day to give compound **2** as colorless crystals.

References: V. Y. Sosnovskikh, R. A. Irgashev, *Tetrahedron Lett.*, **48**, 7436 (2007).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: pyrazolo[1,5-*a*]pyrimidine, 5-amino-1*H*-pyrazole, cyclocondensation

**Experimental procedures:**

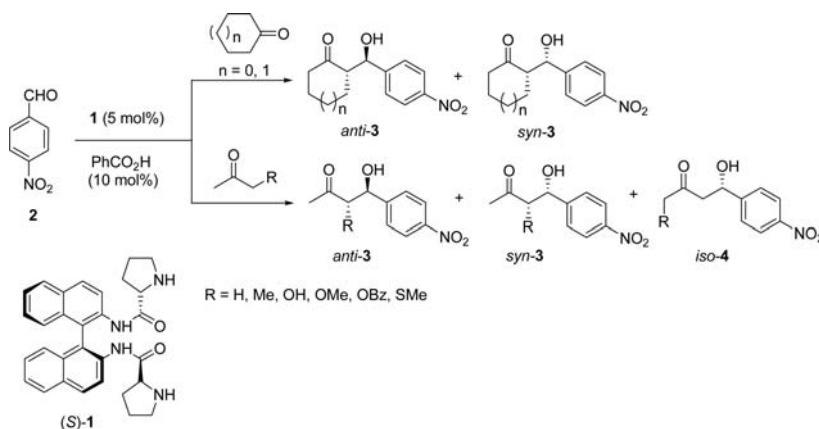
A mixture of equimolar amounts of 5-amino-3-R-1*H*-pyrazole **1** (1 mmol) and 3-(3-oxo-2-benzofuran-1(3*H*)-ylidene) pentane-2,4-dione **2** (230 mg, 1 mmol) was heated in an oil-bath at 150 °C for 1.5–2 min. It was then stirred and allowed to cool to room temperature till it solidified. The solid material was treated with ethanol. After the solvent was removed the products formed were recrystallized from ethanol.

References: J. Quiroga, J. Portilla, R. Abonia, B. Insuasty, M. Nogueras, *Tetrahedron Lett.*, **48**, 6352 (2007).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: aldol reaction, (S)-binam-L-prolinamide



Experimental procedures:

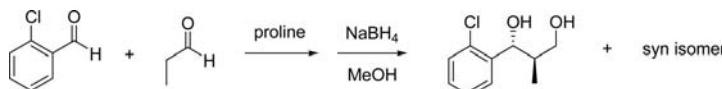
4-Nitrobenzaldehyde (0.25 mmol), ketone (2 equiv.) (Sa)-binam-L-Pro **1** (5 mol%) and benzoic acid (10 mol%) were mixed at 0 °C, unless otherwise stated. After completion of the reaction, performed under magnetic stirring, 1 M HCl (10 mL) and ethyl acetate (20 mL) were added. The organic phase was separated, dried and evaporated to afford the crude products, which were purified by flash chromatography.

References: G. Guillena, M. del Carmen, C. Najera, S.F. Viozquez, *Tetrahedron: Asymmetry*, **18**, 2300 (2007).

Type of reaction: C–C bond formation

Reaction condition: solvent-free

Keywords: aldol reaction, proline



Experimental procedures:

To a mixture of *o*-chlorobenzaldehyde (45 L, 0.4 mmol) and L-proline (5 mg, 0.04 mmol) was added propanal (144 L, 2.0 mmol) at 0 °C. After stirring the reaction mixture for 48 h at that temperature, it was cooled to 0 °C and MeOH (1 mL) and NaBH_4 (76 mg, 2.0 mmol) were added. The reaction mixture was stirred for 1 h at 0 °C. The reaction was quenched with pH 7.0 phosphate buffer

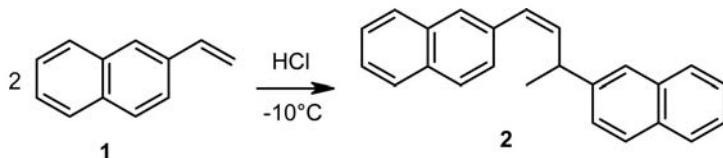
solution and the organic materials were extracted with ethyl acetate three times and then the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* after filtration. Purification by preparative thin layer chromatography (ethyl acetate) gave (*1R,2R*)-1-(*o*-chlorophenyl)-2-methylpropane-1,3-diol (72 mg, 0.36 mmol) in 90% yield as the diastereomeric mixture (anti:syn = 12.9:1). The enantiomeric excess of *anti*-aldol was 96% ee.

References: Y. Hayashi, S. Arataka, T. Itoh, T. Okano, T. Sumiya, M. Shoji, *Chem. Comm.*, 957 (2007).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: solid-gas reaction, quantitative, acid catalysis, linear dimerization, 2-vinylnaphthalene, stereospecific



Experimental procedure:

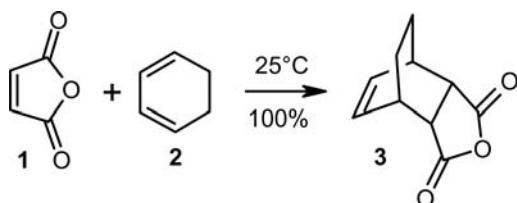
2-Vinylnaphthalene (1.00 g) was cooled to -10°C in an evacuated 100-mL flask and HCl gas (1 bar) was added from a lecture bottle and left at that temperature overnight. The pure product **2** was obtained quantitatively after collection of the HCl gas for recovery from a trap at 77 K, followed by thawing to room temperature and further evacuation for 2 h.

References: G. Kaupp, *Top. Curr. Chem.* **254**, 95 (2005).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: solid-gas reaction, Diels-Alder reaction, maleic anhydride, 1,3-cyclohexadiene, quantitative, stereospecific



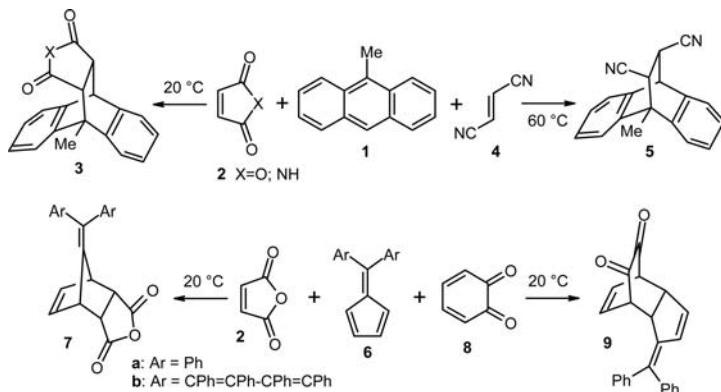
Experimental procedure:

Freshly distilled 1,3-cyclohexadiene **2** (210 mg, 2.23 mmol) in an evacuated 50-mL flask at 15 °C was connected to an evacuated 50-mL flask with freshly sublimed **1** (218.5 mg, 2.23 mmol) at 20 °C. The vacuum tight arrangement was left at these temperatures for 6 h to obtain pure **3** in quantitative yield.

References: G. Kaupp, *Top. Curr. Chem.* **254**, 95 (2005).

Type of reaction: C–C bond formation**Reaction condition:** solid-state

Keywords: solid-solid reaction, Diels-Alder reactions, maleic anhydride, fumaro-dinitrile, fumarodinitrile, fulvenes, orthoquinone, 9-methylanthracene, ball mill, stereospecific, stereospecific

**Experimental procedure:**

9-methylanthracene **1** (2.00 mmol) and **2** (2.00 mmol) or **4** (2.00 mmol) were ball-milled for 1 h at 20 °C or 60 °C, respectively. A quantitative yield (100%) of pure **3** or **5** was obtained. Only the synthesis of **5** passed through a softened phase by kneading at that temperature.

The fulvenes **6** (2.00 mmol) and **2** (2.00 mmol) or **8** (2.00 mmol) were ball-milled for 1 h at 20 °C. A quantitative yield (100%) of pure **7** or **9** was obtained.

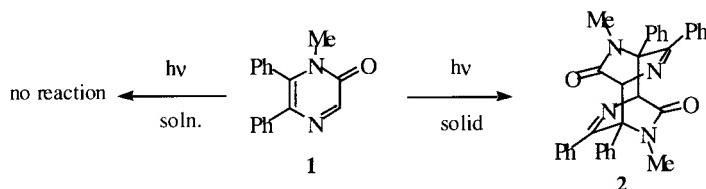
References: G. Kaupp, *Top. Curr. Chem.* **254**, 95 (2005).

3.2 Solvent-Free C–C Bond Formation under Photoirradiation

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 1-methyl-5,6-diphenyl-2-pyrazinone, [4+4]photodimerization



Experimental procedures:

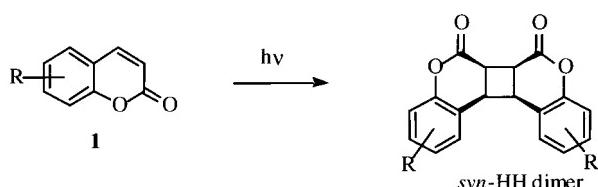
Irradiation of **1** in the solid state with a high-pressure mercury lamp (400 W) at room temperature for 20 min gave the [4+4] *anti* dimer **2**, mp 148–150 °C, in 100% yield based on recovered starting pyrazinone **1**.

References: T. Nishio, N. Nakajima, Y. Omote, *Tetrahedron Lett.*, **21**, 2529 (1980).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: coumarin, [2+2]photodimerization, cyclobutane



- a: R=6-methoxy
- b: R=7-methoxy
- c: R=8-methoxy
- d: R=6-acetoxy
- e: R=7-acetoxy
- f: R=4-methyl-7-acetoxy
- g: R=6-chloro
- h: R=7-chloro
- i: R=4-methyl-6-chloro
- j: R=4-methyl-7-chloro
- k: R=7-methyl

Experimental procedures:

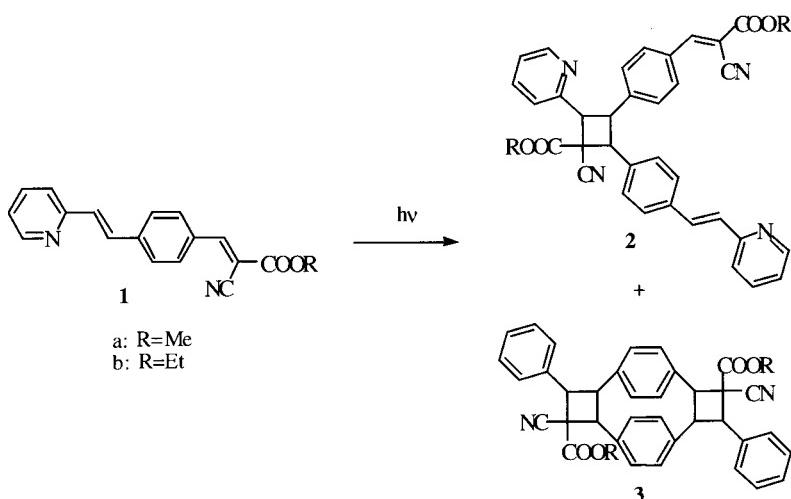
Powdered single crystals of coumarins kept in a petri dish were irradiated with a Hanovia 450-W medium-pressure mercury arc lamp from a distance of about 2 ft. Samples were turned around periodically to provide uniform exposure. Progress of the irradiation was monitored by variation in melting point and ¹H NMR and IR spectra. After complete conversion, the time of which was dependent on the nature of the coumarin, the dimer was separated from the monomer by TLC. Dimers were identified by their spectral properties.

References: K. Gnanaguru, N. Ramasubbu, K. Venkatesan, V. Ramamurthy, *J. Org. Chem.*, **50**, 2337 (1985).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *a*-cyano-4-[2-(2-pyridyl)ethenyl]cinnamate, [2+2]photodimerization, cyclobutane, [2.2]paracyclophane

**Experimental procedures:**

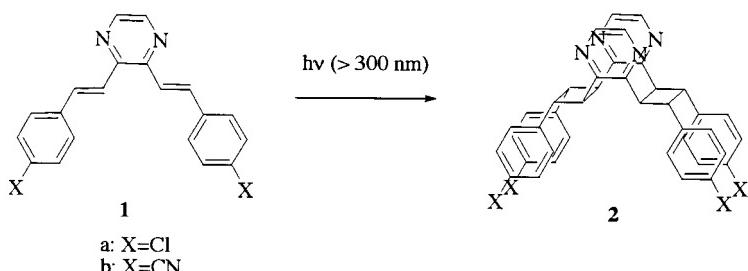
Finely powdered monomer crystals were dispersed in distilled water containing a few drops of surfactant and irradiated, with vigorous stirring, by a 500-W super-high-pressure mercury lamp set outside of the flask. Dimers **2** were prepared by the irradiation of crystals **1** with $\lambda > 410 \text{ nm}$, and by successive purification by preparative TLC. [2.2]Paracyclophane **3a** was obtained by the photoirradiation of **1a** crystals with $\lambda > 300 \text{ nm}$ at -40°C , followed by successive washing with ethyl acetate.

References: C. Chung, A. Kunita, K. Hayashi, F. Nakamura, M. Hasegawa, *J. Am. Chem. Soc.*, **113**, 7316 (1991).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 2,3-di[(E)-styryl]pyrazine, [2+2]photodimerization



Experimental procedures:

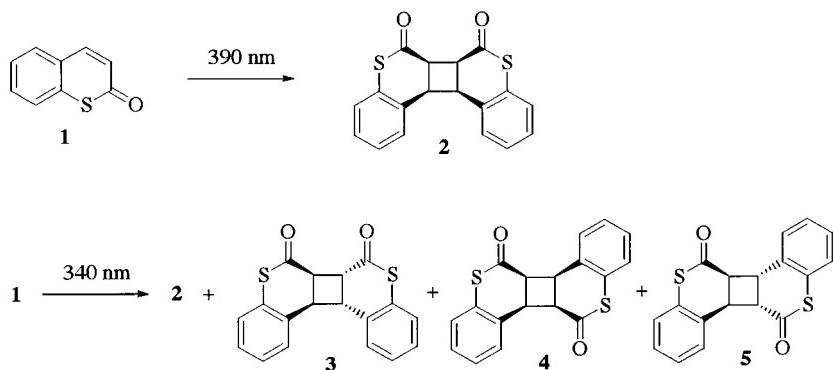
Finely powdered crystals of **1** (100 mg) were dispersed in 100 mL of water containing a few drops of a surfactant (Nikkol TL-10FF) and irradiated from outside the flask with a 500-W super-high-pressure mercury lamp (Ushio USH 500 D) through an optical filter (Kenko UV-32 (cut off nm)) with vigorous stirring under a nitrogen atmosphere. The products were separated and purified by preparative TLC (dichloromethane).

References: A. Takeuchi, H. Komiya, T. Yukihiko, Y. Hashimoto, M. Hasegawa, Y. Iitaka, K. Siago, *Bull. Chem. Soc. Jpn.*, **66**, 2987 (1993).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: thiocoumarin, [2+2]photodimerization, cyclobutane



Experimental procedures:

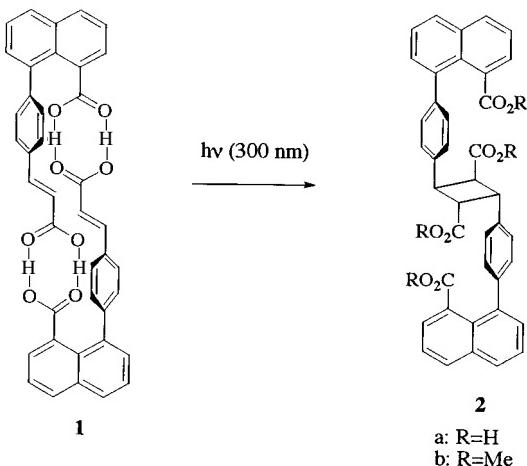
A solution of 81 mg (0.5 mmol) of **1** in 10 mL of Et₂O (25 mL tapered flask) is slowly evaporated to produce a homogeneous solid film. The flask is then purged with Ar, fixed next to the immersion wall (filter A) of the lamp and turned around from time to time. After 140 h, chromatography (SiO₂/CH₂Cl₂) affords first 49 mg of **1** and then 25 mg (30 %) of **2**.

References: C.P. Klaus, C. Thiemann, J. Kopf, P. Margaretha, *Helv. Chim. Acta.*, **78**, 1079 (1995).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: cinnamic acid derivative, [2+2]photodimerization, α -truxillic acid, cyclobutane



Experimental procedures:

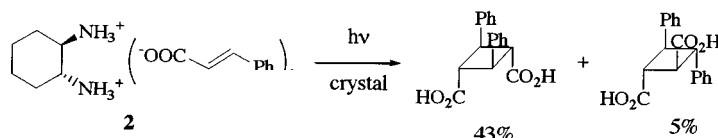
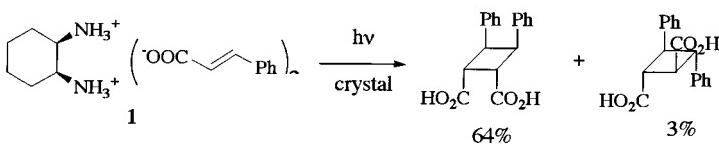
Irradiation of a recrystallized sample (10–15 mg) of **1** through Pyrex in a Rayonet carousel photoreactor (300 nm) led to clean conversion of the starting material into a single cyclobutane product over the course of 20–50 h. The original colorless crystals visibly yellowed and lost definition around the sharp edges during irradiation but did not shatter or crumble. Treatment of the crude solid reaction product with etherial diazomethane permitted isolation of the cyclobutane product **2b** which was shown to have the *α*-truxillate-type stereochemistry.

References: K. S. Feldman, R. F. Campbell, *J. Org. Chem.*, **60**, 1924 (1995).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *trans*-cinnamic acid, double salt formation, [2+2]photodimerization, truxillic acid, truxinic acid, cyclobutane



Experimental procedures:

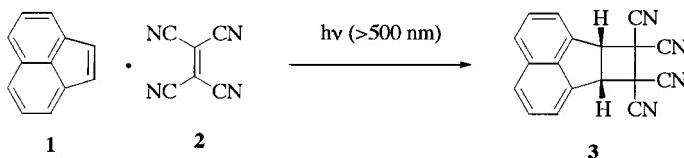
A white powder (158 mg) obtained from photolysis of the double salt **2** was fractionally recrystallized by using 10 mL of methanol, resulting in the isolation of pure colorless plates of the 1:1 (from NMR) ϵ -truxillic acid *trans*-1,2-diaminocyclohexane salt; yield 57 mg, mp 146–150 °C. In addition, 2 mg of white crystals of the 1:1 δ -truxillic acid *trans*-1,2-diaminocyclohexane salt contaminated with a small amount of the above double salt was obtained. Free δ -truxillic acid was recovered by dissolving 3 mg of the double salt in 1 mL of water, followed by acidifying the solution with 1 M HCl to pH 1, as white needles (1.5 mg), mp 200–202 °C (lit. mp 192 °C).

References: Y. Ito, B. Borecka, J. Trotter, J.R. Scheffer, *Tetrahedron Lett.*, **36**, 6083 (1995).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: acenaphthylene, tetracyanoethylene, CT complex, [2+2]photocycloaddition, cyclobutane



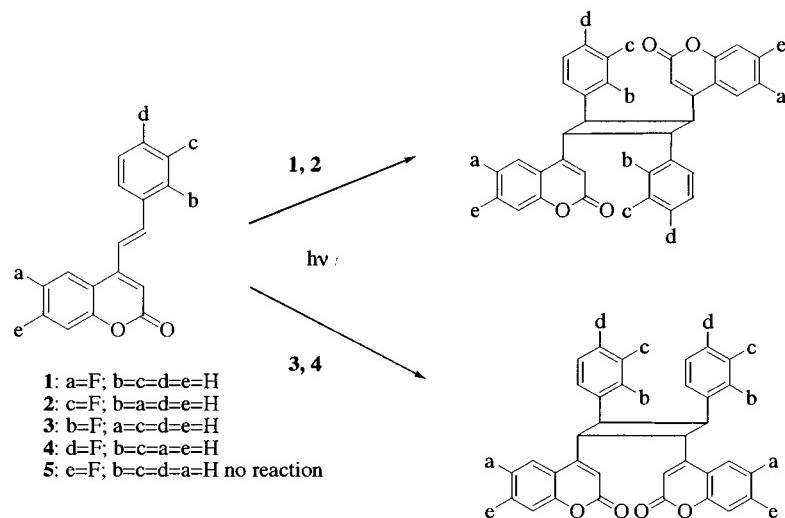
Experimental procedures:

A 40 mg sample of **1·2** placed between two disk glass filters was irradiated using a 400-W high-pressure Hg lamp in a thermostat. The products (**3** and dimers of **1**) and unreacted **1** were isolated by column chromatography. Compound **3** and the dimers of **1** were identified by comparison with authentic samples prepared by alternative methods.

References: N. Haga, H. Nakajima, H. Takayanagi, K. Tokumaru, *Chem. Commun.*, 1171 (1997); N. Haga, H. Nakajima, H. Takayanagi, K. Tokumaru, *J. Org. Chem.*, **63**, 5372 (1998).

Type of reaction: C–C bond formation**Reaction condition:** solid-state

Keywords: fluoro-substituted styrylcoumarin, [2+2]photodimerization, cyclobutane

**Experimental procedures:**

The powder samples of **1** and **2** were irradiated with UV-light in a Rayonet photochemical reactor (λ_{max} 320 nm) at room temperature. The progress of the reaction was monitored by ^1H NMR spectroscopy and TLC. Corresponding photodimers were purified by column chromatography using 10% EtOAc in light petroleum.

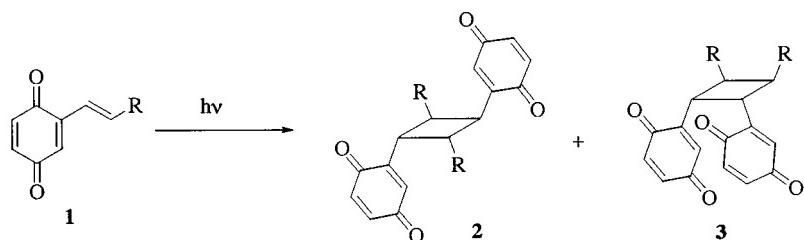
References: K. Vishnumurthy, T.N.G. Row, K. Venkatesan, *J. Chem. Soc., Perkin Trans. 2*, 1475 (1996); K. Vishnumurthy, T.N.G. Row, K. Venkatesan, *J. Chem. Soc., Perkin*

Trans. 2, 615 (1997); K. Vishnumarthy, T.N.G. Row, K. Venkatesan, *Photochem. Photobiol. Sci.*, **1**, 799 (2002).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: vinylquinone, [2+2]photodimerization, 1,4-benzoquinone, cyclobutane



Experimental procedures:

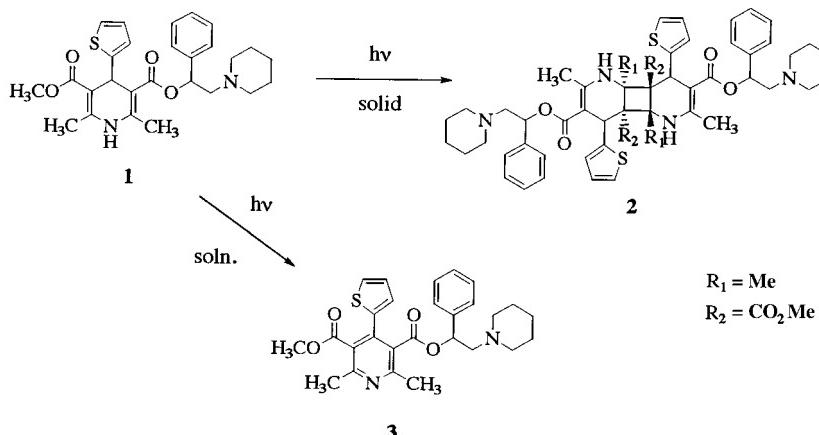
The irradiation of 200–400 mg of the powdered derivatives **1** were carried out with a 1200-W high-pressure mercury lamp in a glass vessel at 20°C for 5 h with continuous stirring. The melting range of the irradiated quinones was raised by 35–70°C. For removal of unreacted starting materials and isolation of the generated photoproducts, the mixture was treated with a suitable solvent at room temperature. After recrystallization, the yellow cyclobutanes were obtained in analytical purity.

References: H. Irngartinger, B. Stadler, *Eur. J. Org. Chem.*, **605** (1998).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 1,4-dihydropyridine, [2+2]photodimerization, cyclobutane



Experimental procedures:

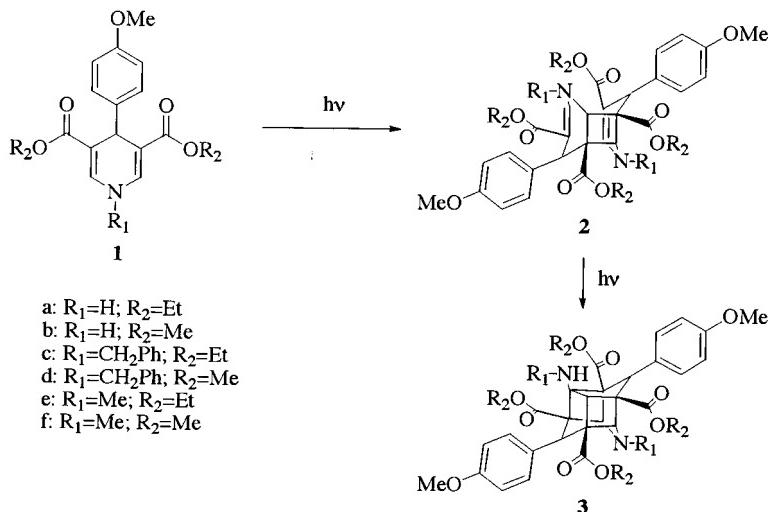
Photolyses were performed at room temperature using a Nagano Science LT-120 irradiator equipped with a Toshiba chemical lamp FIR-20S-BL/M (800 mW cm⁻²). The crystalline samples were packed between two glass plates and placed in the irradiator. The time course of the reaction was checked by HPLC periodically. Irradiation of **1** for 3 h afforded the photoproduct **2** in 100% yield. The pyridine derivatives of **1** and **3** were identified by means of HPLC analyses using photodiode array detection by comparison of the retention time and the UV spectra to those of the authentic samples.

References: N. Marubayashi, T. Ogawa, T. Hamasaki, N. Hirayama, *J. Chem. Soc., Perkin Trans. 2*, 1309 (1997); N. Marubayashi, T. Ogawa, N. Hirayama, *Bull. Chem. Soc. Jpn.*, **71**, 321 (1998).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 1,4-dihydropyridine, [2+2]photodimerization, cyclobutane



Experimental procedures:

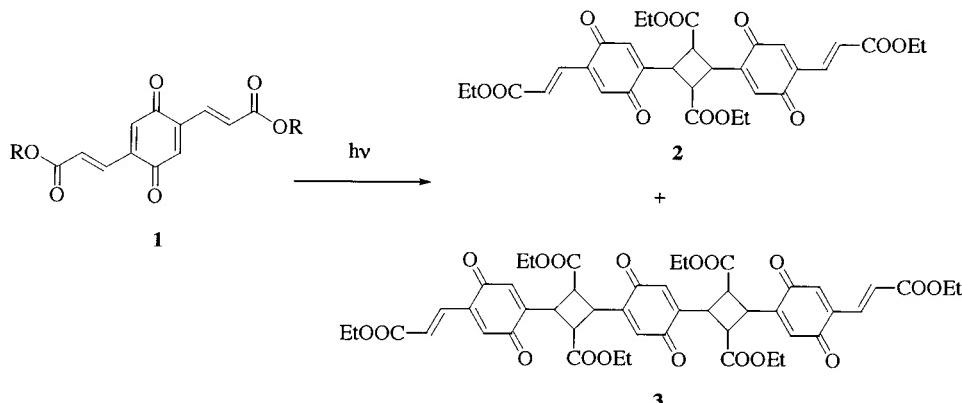
1 g of crystalline 1,4-dihydropyridine **1** with a layer thickness of 1 mm was irradiated with an Ultra-Vitalux lamp from a distance of 60 cm at a measured temperature of 25 °C. After 3–4 d of irradiation (product formation monitored by TLC) the products **2** and **3**, were dissolved in boiling toluene and ethanol, respectively, from which they crystallized. The following yields are based on 1 g of **1**, corresponding to a 100% yield of **3** obtained by the direct irradiation of **1**.

References: A. Hilgeroth, U. Baumeister, F.W. Heinemann, *Eur. J. Org. Chem.*, 1213 (1998); A. Hilgeroth, *Chem. Lett.*, 1269 (1997).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 2,5-bis(2-alkoxycarbonylethenyl)-1,4-benzoquinone, [2+2]photodimerization, cyclobutane

**Experimental procedures:**

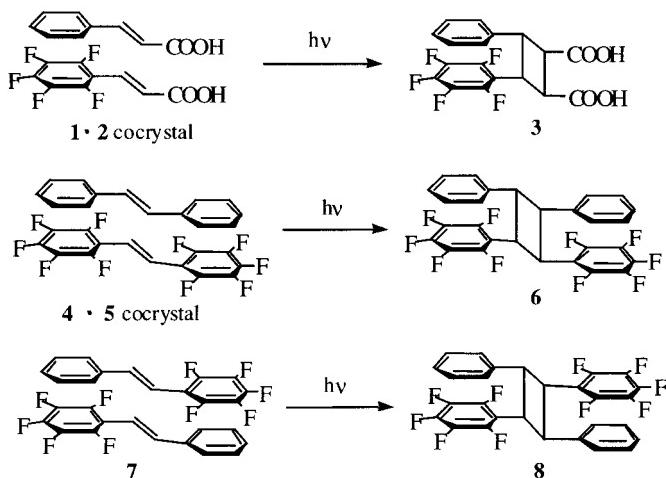
The powdered quinones were dispersed homogenously in a dish made of aluminum foil and covered with the appropriate filter. All quinones were irradiated successively under dried nitrogen for 4 h at 20 °C.

References: H. Irngartiger, R. Herpich, *Eur. J. Org. Chem.*, 595 (1998).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *trans*-stilbene, cinnamic acid, [2+2]photodimerization, photopolymerization, cyclobutane



Experimental procedures:

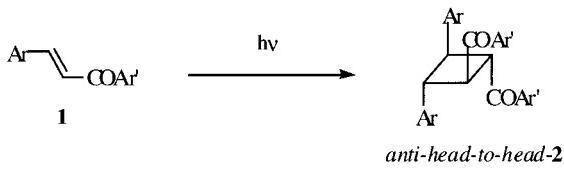
trans-Cinnamic acid (**1**, 1.00 g, 6.75 mmol) and *trans*-2,3,4,5,6-pentafluorocinnamic acid (**2**, 1.61 g, 6.75 mmol) were dissolved in 8 mL of hot absolute ethanol. The solution was allowed to cool slowly to room temperature, during which fine white crystals were formed. After crystallizing overnight, the cocrystals were collected by filtration and dried in *vacuo* to give cocrystal **1·2** (2.45 g, 94%). Crystals of **1·2** (20.0 mg) were placed in a quartz reaction tube and photolyzed for 7 h at ambient temperature. ^1H NMR spectroscopy revealed the cyclodimer **3** (87%).

References: G. W. Coates, A. R. Dunn, L. M. Henling, J. W. Ziller, E. B. Lobkovsky, R. H. Grubbs, *J. Am. Chem. Soc.*, **120**, 3641 (1998).

Type of reaction: C–C bond formation

Reaction condition: molten-state

Keywords: chalcone, [2+2]photodimerization, molten-state, cyclobutane



- a: Ar=Ph; Ar'=Ph
- b: Ar=Ph; Ar'=4-MeC₆H₄
- c: Ar=Ph; Ar'=4-ClC₆H₄
- d: Ar=4-MeOC₆H₄; Ar'=Ph
- e: Ar=4-MeC₆H₄; Ar'=4-MeC₆H₄

Experimental procedures:

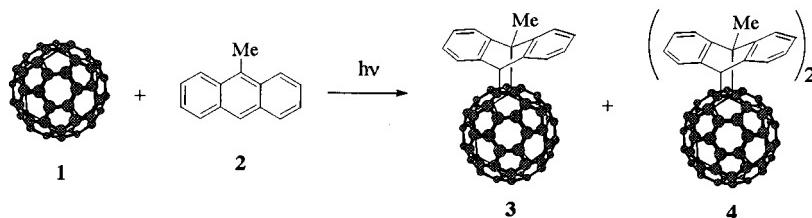
Chalcone **1a** (1 g, 4.8 mmol) was placed in between two Pyrex plates and the sample was melted by being heated at 60 °C on a hot-plate, and thereafter was irradiated with a 400-W high-pressure Hg lamp for 24 h. The oily crude product was crystallized by addition of a small amount of MeOH to give, after recrystallization from MeOH, compound **2a** as prisms (0.31 g, 31%), mp 123–125 °C.

References: F. Toda, K. Tanaka, M. Kato, *J. Chem. Soc., Perkin Trans. 1*, 1315 (1998).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 9-methylanthracene, C₆₀, fullerene, Diels-Alder reaction, photoirradiation

**Experimental procedures:**

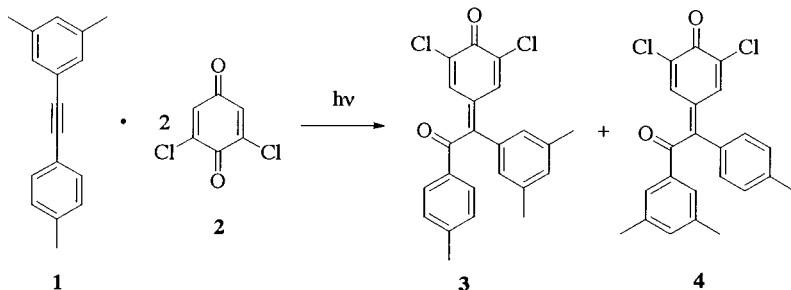
A well ground mixture of C₆₀ **1** and 9-methylanthracene **2** (1:1) was exposed to high-pressure mercury lamp through Pyrex vessel with stirring by using cooling jacket to keep the reaction temperature at 28°C. The reaction mixture was then dissolved in C₆D₆/CS₂ and yields of mono- and bis-adducts were determined by ¹H NMR analysis using triptycene as an internal standard.

References: K. Mikami, S. Matsumoto, T. Tonoi, Y. Okubo, *Tetrahedron Lett.*, **39**, 3733 (1998).

Type of reaction: C-C bond formation

Reaction condition: solid-state

Keywords: diarylacetylene, dichlorobenzoquinone, donor-acceptor complex, photoirradiation

**Experimental procedures:**

To a thin Pyrex tube were added several orange crystals (7 mg, 0.012 mmol) of EDA complex (**1·2(2)**), and the tube was sealed under an argon atmosphere. The reaction tube was placed in a clear Dewar filled with acetone cooled to -60°C and the sample irradiated with a medium-pressure mercury lamp fitted with an aqueous IR filter and a Corning cutoff filter to effect irradiation with visible light ($\lambda > 410$ nm). The tube was rotated each hour, and the temperature in the Dewar

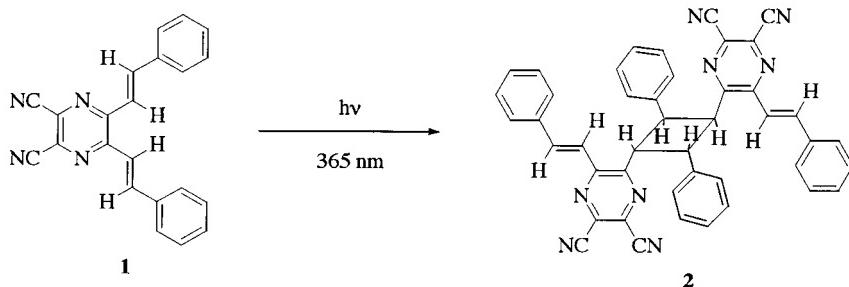
was controlled by the periodic addition of dry ice. After 5 h of irradiation, the crystals extensively cracked. The crystals were dissolved in dichloromethane, and the immediate analysis by quantitative GC. The crude products from several experiments were combined and purified by thin-layer chromatography with hexane-ethyl acetate (10:1) as eluent.

References: E. Bosch, S.M. Hubig, S.V. Lindeman, J.K. Kochi, *J. Org. Chem.*, **63**, 592 (1998).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 2,3-bis(2-phenylethenyl)-4,5-dicyanopyrazine, [2+2]photocycloaddition, cyclobutane



Experimental procedures:

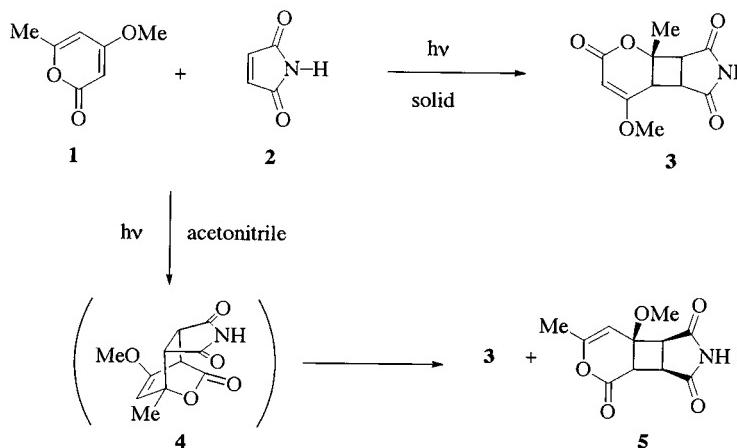
Compound **1** was recrystallized in two different forms; one was yellow colored crystal **1a** (benzene), and the other was orange crystal **1b** (a mixture of THF and acetonitrile). Photoirradiation on **1a** in the single crystals at 366 nm for 15 h gave mainly the insoluble polymer and small amounts of **2**, but **1b** did not react at all.

References: J.H. Kim, M. Matsuoka, K. Fukunishi, *Chem. Lett.*, 143 (1999).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 4-methoxy-6-methyl-2-pyrone, maleimide, [2+2]photocycloaddition, cyclobutane



Experimental procedures:

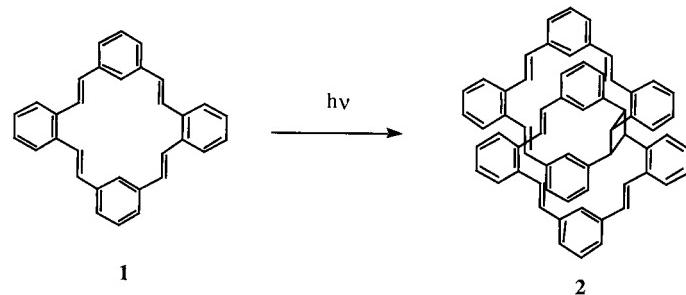
Irradiation of a 1:1 complex crystal (mp 95–97°C, plates) between **1** and **2**, which was prepared by recrystallization of the equimolar substrates from acetonitrile, with a 400-W high-pressure mercury lamp through a Pyrex filter under nitrogen at room temperature gave [2+2]cycloadduct **3** in 54% yield as a sole product. On the other hand, direct photoirradiation to an acetonitrile solution of **1** and **2** gave another type of [2+2]cycloadduct **5** in 25% yield together with a small amount of **3**.

References: T. Obata, T. Shimo, S. Yoshimoto, K. Somekawa, M. Kawaminami, *Chem. Lett.*, **181** (1999); T. Obata, T. Shimo, M. Yasutaka, T. Shimyozu, M. Kawaminami, R. Yoshida, K. Somekawa, *Tetrahedron*, **57**, 1531 (2001); T. Shimo, T. Vezono, T. Obata, M. Yasutake, T. Shimyozu, K. Somekawa, *Tetrahedron*, **58**, 6111 (2002).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: tetrabenzoc[*ab,f,jk,o*][18]annulene, [2+2]photodimerization



Experimental procedures:

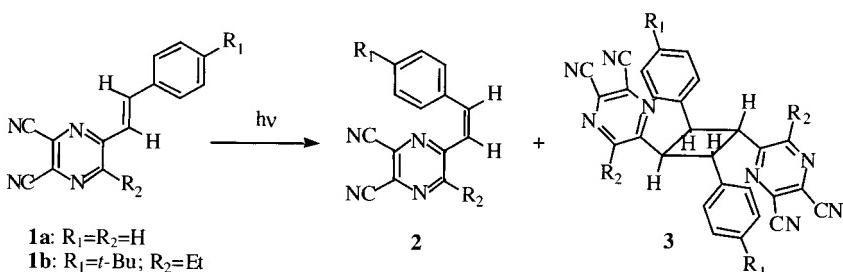
A suspension of 16.0 mg (0.04 mmol) **1** in 500 mL water was circulated through a photoreactor equipped with a 150-W mercury lamp (Hanau TQ 150 Z 3) with a main emission between 300 and 400 nm. After 1 h the irradiation was stopped and the suspension filtered. The dry residue was dissolved in $\text{CDCl}_2\text{-CDCl}_2$. The ^1H NMR spectrum at 50 °C shows the signals of **1** and its dimer **2** in a ratio of 30:70 and a small amount of oligomers. Prolonged irradiation yielded higher amounts of oligomeric material.

References: R. Yu, A. Yakimansky, I.G. Voigt-Martin, M. Fettner, C. Schnorpfeil, D. Schollmeyer, H. Meier, *J. Chem. Soc., Perkin Trans. 2*, 1881 (1999).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: styryldicyanopyrazine, topochemical photodimerization, cyclobutane

**Experimental procedures:**

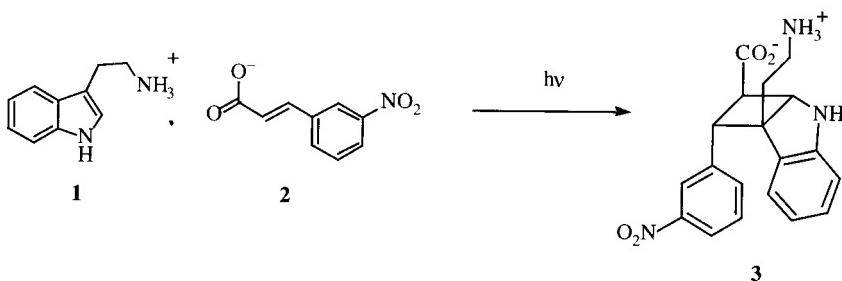
Upon photoirradiation of single crystals of **1a** and **1b** with 366 nm UV light for 15 h a photodimer of **1a** having an anti head-to-head form **3a** was obtained in excellent yield (90%), whereas **1b** gave **3b** in poor yield (17%) together with unreacted **1b** (83%). Neither of **2a** and **2b** were obtained in the solid state.

References: J.H. Kim, M. Matsuoka, K. Fukunishi, *J. Chem. Res. (S)*, 132 (1999).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: tryptamine, 3-nitrocinnamic acid, [2+2]photocycloaddition, cyclobutane



Experimental procedures:

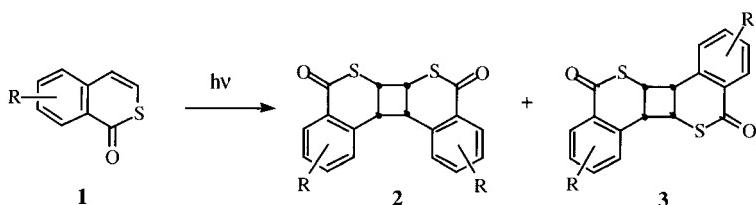
A crystalline salt of **1** and **2** (20 mg) was crushed and spread between two Pyrex plates and this was irradiated with a 400-W high-pressure mercury lamp for 20 h under an argon atmosphere. The irradiation vessel was cooled from the outside by tap water. After the irradiation, the reaction mixture was analyzed by ^1H NMR. The only peaks observable were those for the starting materials (**1** and **2**) and a cross photoadduct (**3**) (47% conversion, 39% yield). In a separate experiment, 105 mg of the salt was irradiated under similar conditions. The product **3** could be isolated simply by fractional recrystallization from ethanol (15 mL). Polymeric products (6 mg) first separated and then 18 mg (17% yield) of nearly pure **3** separated as a pale brown powder: mp 215–225 °C.

References: Y. Ito, H. Fujita, *Chem. Lett.*, 288 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: isothiocoumarin, [2+2]photodimerization, cyclobutane



a: R=H

b: R=7-Me

c: R=5-CF₃

d: R=5,6-C₄H₄

Experimental procedures:

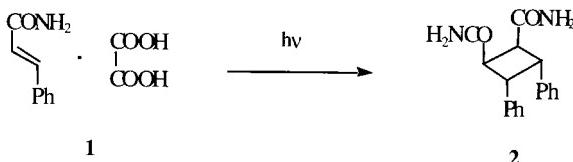
Irradiation (350 nm) of **1b** as homogeneous solid film leads to the selective (94%) formation of the *HH-cis-cisoid-cis* photocyclodimer **2b** and traces (6%) of the *HT-cis-cisoid-cis* dimer **3b** (monitoring by ¹H NMR). Dimer **2b** was isolated and purified by chromatography. Similarly, irradiation of **1c** affords a 4:5 mixture of dimers **2c** and **3c** which were not separated.

References: M. A. Kinder, J. Kopf, P. Margaretha, *Tetrahedron*, **56**, 6763 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *trans*-cinnamamide, dicarboxylic acid, cocrystals, [2+2]photodimerization, cyclobutane

**Experimental procedures:**

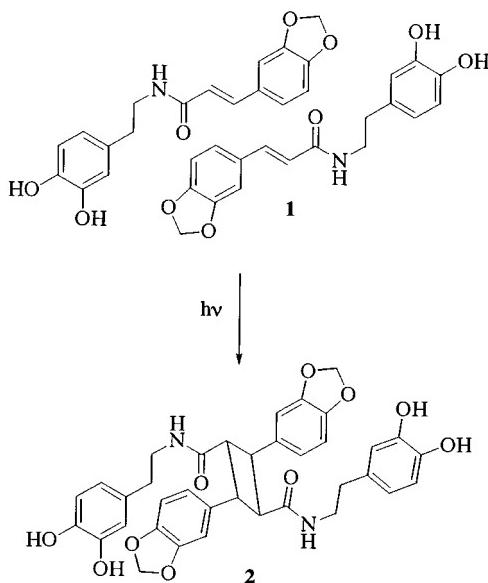
Cocrystal **1** (51 mg) was irradiated for 20 h as described above. The slightly colored photolysate, which contained **2** with 29% yield (estimated by ¹H NMR and HPLC), was taken up in 2 mL of water and was stirred at 45 °C for 1 h. After cooling in a refrigerator, an insoluble pale yellow solid was collected by filtration. This was stirred into 2 mL of acetonitrile and an insoluble solid was filtered off to afford 5 mg (13% yield) of **2** as a white crystalline solid: mp 246–252 °C.

References: Y. Ito, H. Hosomi, S. Ohba, *Tetrahedron*, **56**, 6833 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *N*–[(*E*)-3,4-methylenedioxy cinnamoyl]dopamine, [2+2]photodimerization, cyclobutane

**Experimental procedures:**

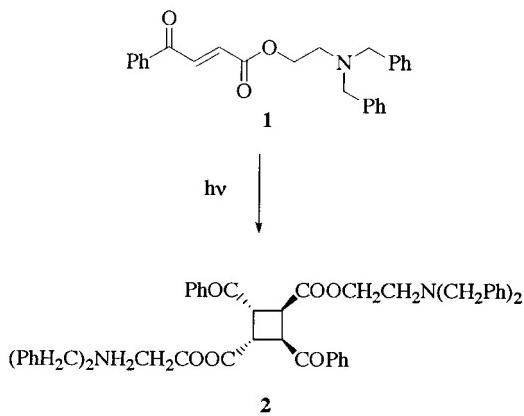
Irradiation of crystalline **1** under an argon atmosphere with a 400-W high-pressure Hg lamp (Pyrex) for 20 h gave **2** (66% conversion, 100% yield).

References: Y. Ito, S. Horie, Y. Shindo, *Org. Lett.*, **3**, 2411 (2001).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 2-(dibenzylamino)ethyl 3-benzoylacrylate, [2+2]photocycloaddition, cyclobutane



Experimental procedures:

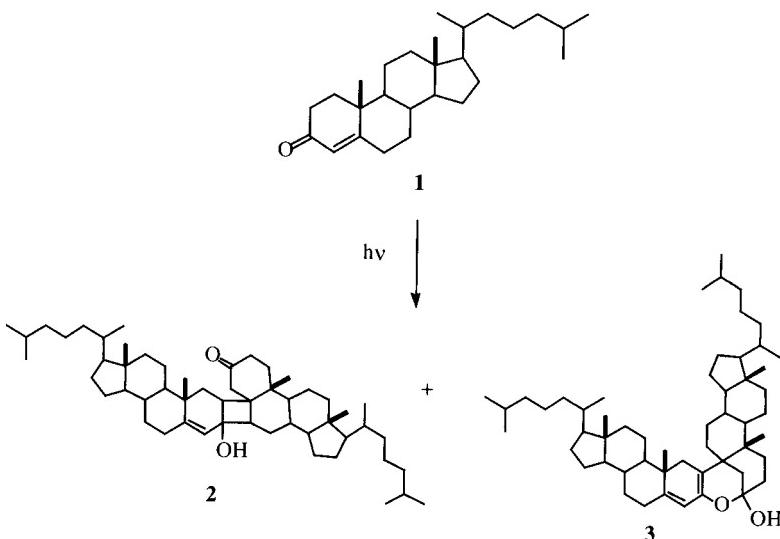
The crystals of **1** (0.635 g, 1.6 mmol) were placed between Pyrex glass plates and irradiated for 75 min with a 400-W high-pressure mercury lamp. After the irradiation the color of the crystals had changed from pale yellow to white and bis[2-(dibenzylamino)ethyl]c-2,4-dibenzoylcyclobutane-*r*-1,4-dicarboxylate **2** was obtained quantitatively: mp 143.0 °C (from a mixture of dichloromethane and hexane).

References: T. Hasegawa, K. Ikeda, Y. Yamazaki, *J. Chem. Soc., Perkin Trans. 1*, 3025 (2001).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: cholest-4-en-3-one, photodimerization, cyclobutane

**Experimental procedures:**

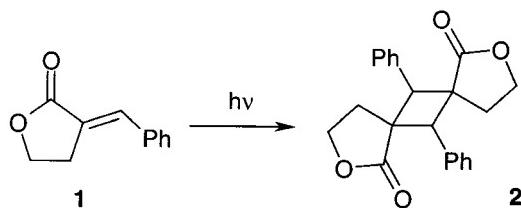
Powdered **1** (200 mg), crystallized from Et₂O, was irradiated with a Hanovia 450-W lamp for 4 h to give a mixture of unreacted **1** (142 mg), **2** (18 mg) and **3** (14 mg) separated by flash chromatography on silica gel (hexane-Et₂O, 19:1).

References: M. DellaGreca, P. Monaco, L. Previtera, A. Zarrelli, A. Fiorentino, F. Giordano, C. Mattia, *J. Org. Chem.*, **66**, 2057 (2001).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: enone, photolysis, [2+2]-cycloaddition, *head-to-tail-anti*, cyclobutane, spiro compound



Experimental procedure:

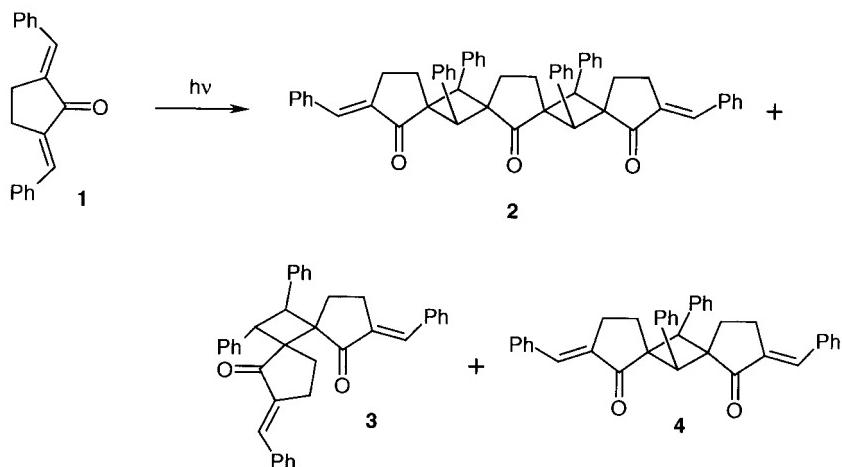
α-Benzylidene- γ -butyrolactone **1** (1.0 g, mp 115–117°C) was evenly spread on the inner wall of a mirrored Dewar vessel (diameter 14 cm, height 20 cm) with some dichloromethane. After heating to 80°C for 1 h the crystalline film was irradiated from within for 5 h with a high-pressure Hg-lamp (Hanovia 450 W) through a 5% solution of benzophenone in benzene (5 mm; $\lambda > 380$ nm) and cooling with running water at 30–35°C. The yield of *head-to-tail-anti*-dimer **2** was quantitative (mp 242°C).

References: G. Kaupp, E. Jostkleigrewe, H.-J. Hermann, *Angew. Chem.*, **94**, 457 (1982); *Angew. Chem. Int. Ed. Engl.*, **21**, 435 (1982). Numerous early solid-state photodimerizations are listed in Houben-Weyl, Methoden der Organischen Chemie, Vol. IV/5a, *Chap. 4 and 5*, pp. 278–412, Thieme, Stuttgart (1975). Further examples are listed in *CRC Handbook of Organic Photochemistry and Photobiology* (Ed. W.M. Horspool), *Chap. 4*, pp. 50–63, CRC Press, Boca Raton (1995).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: enone, photolysis, [2+2]-cycloaddition, cyclobutane, spiro compound



Experimental procedure:

2,5-Bisbenzylidene-cyclopentanone **1** (1.04 g, 2.0 mmol) was evenly spread on the inner wall of a mirrored Dewar vessel (diameter 14 cm, height 20 cm) with some dichloromethane. After heating to 80 °C for 1 h the crystalline film was irradiated from within for 3–5 h at 30–35 °C with a high-pressure Hg-lamp (Hans-via 450 W) through a benzophenone filter (5% in benzene; 5 mm; $\lambda > 380$ nm) and cooling with running water. ^1H NMR-analysis revealed 400 mg (38%) **3**, 275 mg (26%) **2** (structure clarified in Ref. 2), 85 mg (8%) **4** and 190 mg (18%) unreacted **1**. The separation of the products by preparative TLC at 200 g SiO₂ used dichloromethane. Recrystallization of the products was performed in 1,2-dichloroethane, toluene, and methanol, respectively.

References: 1) G. Kaupp, I. Zimmermann, *Angew. Chem.*, **93**, 1107 (1981); *Angew.*

Chem. Int. Ed. Engl., **20**, 1018 (1981).

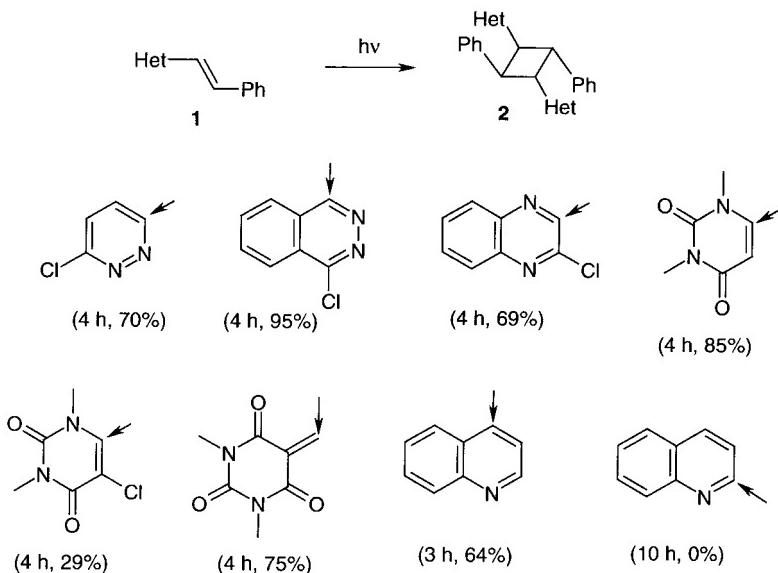
2) G. Kaupp, *J. Microscopy*, **174**, 15 (1994); G. Kaupp, *Mol. Cryst. Liq. Cryst.*, **252**, 259 (1994).

3) Numerous early solid-state photodimerizations are listed in Houben-Weyl, Methoden der Organischen Chemie, Vol. IV/5a, *Chap. 4* and *5*, pp. 278–412, Thieme, Stuttgart (1975). Further examples are listed in *CRC Handbook of Organic Photochemistry and Photobiology* (Ed. W.M. Horspool), *Chap. 4*, pp. 50–63, CRC Press, Boca Raton (1995).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: heterostilbene, [2+2]-cycloaddition, polar effect, photochemistry, cyclobutane



Experimental procedures:

One to three mmol of the polar heterostilbene **1** was spread with some dichloromethane in a sufficiently wide bottom-closed, top-stoppered glass cylinder with gas inlet and outlet to form a 10 cm high zone that matched with the burning zone of a 500-W high-pressure Hg-lamp behind a water cooled Solidex filter. After drying in a vacuum, an even crystal film was obtained. This setup was immersed in a cold bath at 0 °C while the crystal film compartment was filled with argon. Irradiation times varied from 3 to 10 h. The indicated yields were obtained after recrystallization. There were no different stereoisomers of **2** except when the phenyl group was replaced by *p*-nitrophenyl- or *p*-cyanophenyl-groups or if the Het-group was replaced by methoxycarbonyl- or acetyl-groups in 1,2- bifunctional derivatives ($\text{MeO}_2\text{CCH}=\text{CHPhCH}=\text{CHCO}_2\text{Me}$, $\text{AcCH}=\text{CHPhCH}=\text{CHAc}$).

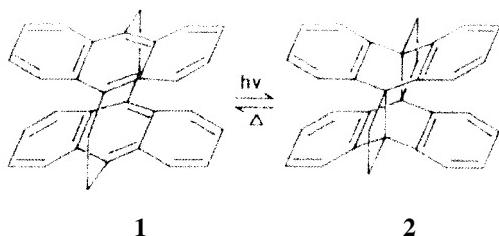
References: G. Kaupp, H. Frey, G. Behmann, *Chem. Ber.*, **121**, 2135 (1988).

Numerous early solid-state photodimerizations are listed in Houben-Weyl, Methoden der Organischen Chemie, Vol. IV/5a, *Chap. 4* and *5*, pp. 278–412, Thieme, Stuttgart (1975). Further examples are listed in *CRC Handbook of Organic Photochemistry and Photobiology* (Ed. W.M. Horspool), *Chap. 4*, pp. 50–63, CRC Press, Boca Raton (1995).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: anthracenophane, [4+4]-dimerization, [4+4]-cycloreversion, photochrome, topotaxy, photochemistry



Experimental procedures:

The golden yellow crystals of **1** were exposed to glass-filtered daylight and thus formed the colorless “dimer” structure **2** with quantitative yield. If **2** was heated to 30°C in the dark for 5 h compound **1** was quantitatively formed back in a topoctic manner without change of the crystal shape even on the nanoscopic scale as shown by atomic force microscopy (AFM). Numerous cycles were performed without loss using single crystals of **1/2** as well.

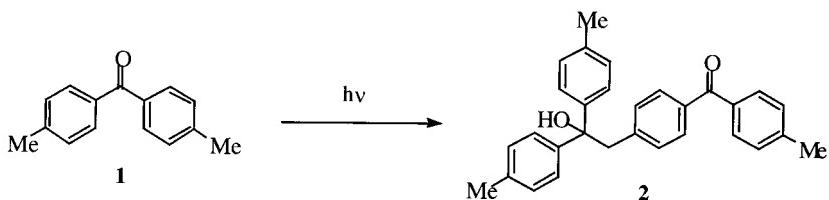
References: G. Kaupp, *Current Opinion in Solid State and Materials Science*, **6**, 131 (2002); *Adv. Photochem.*, **19**, 119–177 (1995); *Liebigs Ann. Chem.*, 844 (1973); D.A. Dougherty, C.S. Choi, G. Kaupp, A.B. Buda, J.M. Rudzinski, E. Osawa, *J. Chem. Soc. Perkin Trans. 2*, 1063 (1986).

Numerous earlier solid-state [4+4]-photodimerizations of solid (substituted) anthracenes are cited there and mechanistically interpreted on the basis of supermicroscopic AFM data.

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 4,4'-dimethylbenzophenone, photodimerization



Experimental procedures:

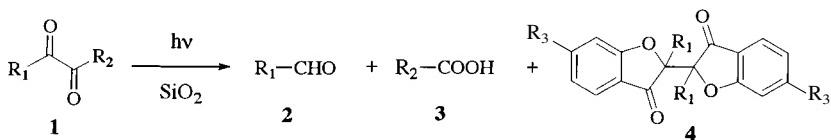
Crystals of **1** were ground to a fine powder in a mortar. The powder (210 mg) was placed between two Pyrex disks (8 cm diameter) and irradiated under a nitrogen atmosphere for 10 h at 0 °C (ice-water) by using a 400-W high-pressure mercury lamp as a light source. The separation between the lamp and the sample was approximately 5 cm. The reaction mixture was separated by preparative TLC to give 178 mg of the recovered **1** and 31 mg (~ 100% yield) of a dimeric product, 4-(2-hydroxy-2,2-di-*p*-tolylethyl)-4'-methylbenzophenone **2**. This was recrystallized from hexane-ethyl acetate (10:1, v/v) to give colorless crystals: mp 53–55 °C.

References: Y. Ito, T. Matsuura, K. Tabata, M. Ben, *Tetrahedron*, **43**, 1307 (1987).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: α -diketone, silica gel surface, Norrish type I reaction, photoreaction



- a: $R_1=R_2=Ph$
 - b: $R_1=R_2=p\text{-MeC}_6H_4$
 - c: $R_1=Me; R_2=Ph$
 - d: $R_1=R_2=Me$
 - e: $R_1=R_2=p\text{-MeOC}_6H_4$

Table 1. Yields of photoproducts.

Yields (%)				
	1	2	3	4
a		Trace	59	16
b		Trace	41	23
c		60	60	0
d		30	0	—
e		0	0	0

Experimental procedures:

The α -diketone **1** (ca. 2.0 mmol) in dichloromethane (5 mL) was added to silica gel (5 g) in a 100-mL round-bottomed flask. The mixture was sonicated for 5 min after which the solvent was evaporated under reduced pressure. The coated silica gel, divided into six nearly equal portions, was then placed in Pyrex tubes (18×180 mm). In the experiments under oxygen-free conditions the tubes were degassed by three freeze-pump-thaw cycles and sealed. The tubes were rotated and irradiated for 48 h with a 100-W high-pressure mercury lamp. The irradiated silica gel was collected. Acetone (20 mL) was added to the silica gel to extract

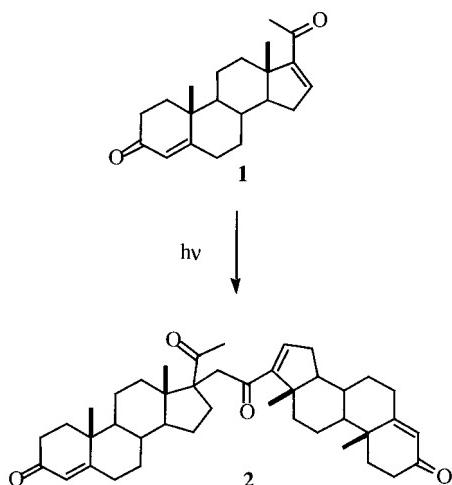
the organic components and the mixture was sonicated for 10 min. The silica gel was filtered off and washed with acetone (10 mL). The combined filtrate and washings were then evaporated under reduced pressure. More than 93% of organic material based on the weight of the starting diketone used was recovered by this method. The residue was chromatographed on silica gel. Elution with a mixture of acetone-hexane (1:6, v/v) gave unchanged diketone and photoproducts (Table 1).

References: T. Hasegawa, M. Imada, Y. Imase, Y. Yamazaki, M. Yoshioka, *J. Chem. Soc., Perkin Trans. 1*, 1271 (1997).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 16-dehydroprogesterone, photodimerization



Experimental procedures:

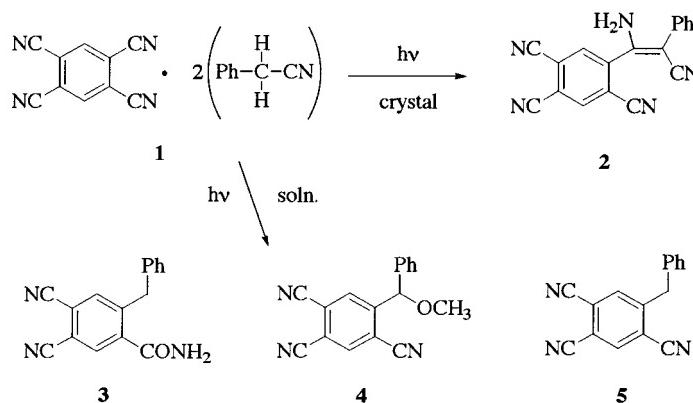
An aqueous suspension (50 mL) of 16-dehydroprogesterone **1** (100 mg) in a Pyrex flask was irradiated with fluorescent lamp (Philips, TLD 30W/55) under magnetic stirring at 24 °C for 10 days. EtOAc extraction and flash chromatography (silica gel, EtOAc-hexane 3:2) followed by preparative TLC gave **2** (20 mg) as a colorless oil.

References: M. DellaGreca, P. Monaco, L. Previtera, A. Fiorentino, F. Giordano, C. Mattia, *J. Org. Chem.*, **64**, 8976 (1999).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: tetracyanobenzene, benzyl cyanide, two-component crystal, photo-reaction



Experimental procedures:

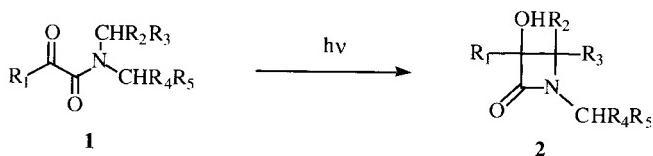
The crystals of **1** (40 mg) were spread between two Pyrex plates and irradiated with a 400-W high-pressure mercury lamp for 20 h under argon. During the irradiation, the photolysis vessel was cooled from the outside by circulation of cold water (4 °C). After the irradiation, the orange photolysate was immediately evaporated in vacuo at 60 °C to remove unreacted BzCN. The residue, where **2** was present as a sole product in 65% yield on the basis of TCNB, was fractionally recrystallized with MeCN (0.6 mL) to furnish 3 mg of pure **2** as orange-yellow plates: mp >300 °C.

References: Y. Ito, S. Endo, S. Ohba, *J. Am. Chem. Soc.*, **119**, 5974 (1997); Y. Ito, H. Nakabayashi, S. Ohba, H. Hosomi, *Tetrahedron*, **56**, 7139 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *N,N*-dialkyl-*a*-oxoamide, Norrish type II reaction, photoirradiation, β -lactam



- a: R₁ = Ph, R₂ = R₄ = H, R₃ = R₅ = Ph
- b: R₁ = Me, R₂ = R₄ = H, R₃ = R₅ = Ph
- c: R₁ = Ph, R₂ = R₃ = R₄ = R₅ = Me
- d: R₁ = Ph, R₂ = R₄ = H, R₃, R₅ = -(CH₂)₃-
- e: R₁ = R₂ = R₃ = R₄ = R₅ = Me

Experimental procedures:

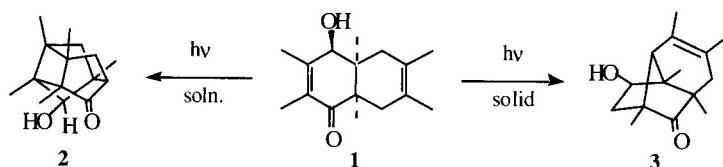
The recrystallized *α*-oxoamide **1** (100–300 mg) was sandwiched between a pair of Pyrex plates (thickness 2 mm) and put into a polyethylene envelope. The envelope was sealed and placed in a cold medium (water, ice-water, or dry ice-methanol) and irradiated with a high-pressure mercury lamp (100 W) for 1–10 h. The lamp was used with a vessel for immersion type irradiation which contained dry air. The products were isolated by column chromatography on silica gel.

References: H. Aoyama, T. Hasegawa, Y. Omote, *J. Am. Chem. Soc.*, **101**, 5343 (1979).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: cyclohexenone, photorearrangement, intramolecular allylic hydrogen abstraction



Experimental procedures:

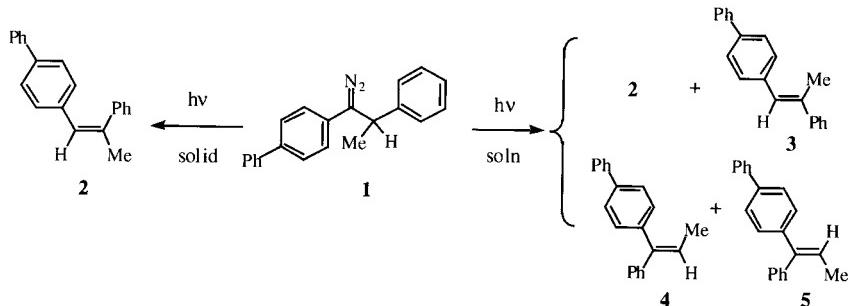
The preparative solid-state photolyses were carried out either on the inner surface of an immersion well apparatus (method A) or by using Pyrex glass plate “sandwiches” sealed in polyethylene bags (method B). Naphthoquinol **1** (70 mg) was irradiated through a uranium glass filter sleeve ($\lambda > 330$ nm) by method A at -74°C under nitrogen for 2.1 h. Column chromatography (silica gel, 20% ethyl acetate-toluene) afforded 39 mg of starting material and 25 mg (81% based on unrecovered starting material) of a new photoproduct **3**.

References: W.K. Appel, Z.Q. Jiang, J.R. Scheffer, L. Walsh, *J. Am. Chem. Soc.*, **105**, 5354 (1983).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: carbene, photorearrangement



Experimental procedures:

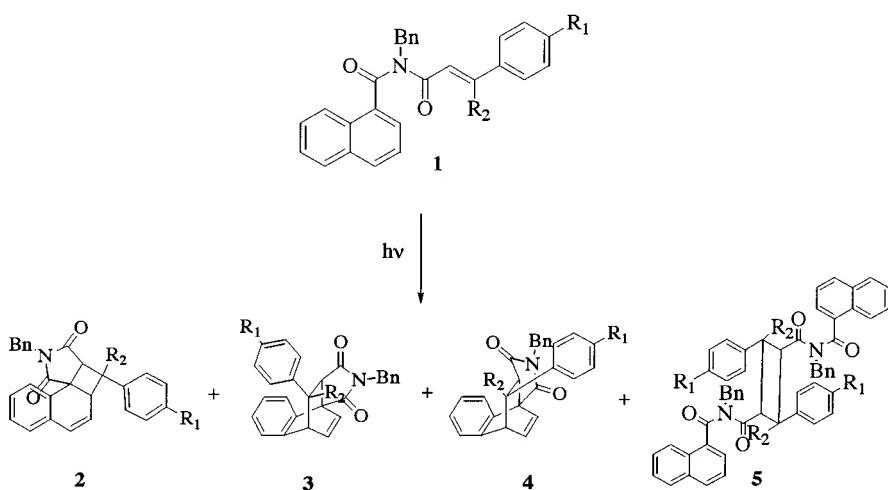
Pure powdered samples of **1** irradiated at 0 °C with $\lambda > 380$ nm showed that compound **2** constitutes over 96% of the product mixture. Product **2** melts at 105 °C.

References: S.H. Shin, A.E. Keating, M.A. Garibay, *J. Am. Chem. Soc.*, **118**, 7626 (1996).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *N*-cinnamoyl-1-naphthamides, [2+2], [4+2]photodimerization, cyclobutane



Experimental procedures:

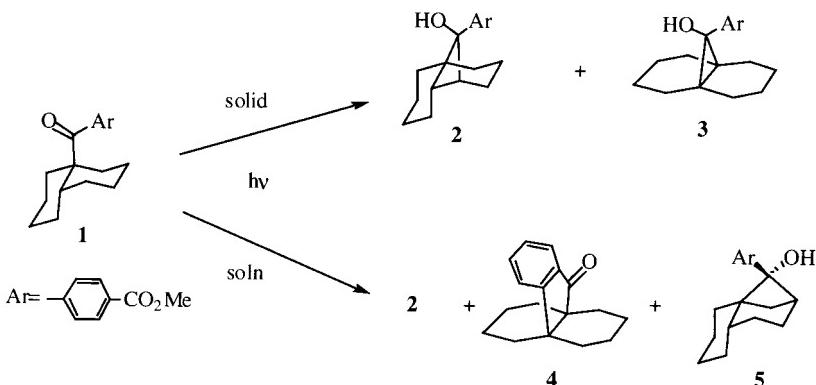
Compound **1** (0.25 mmol) was ground to a powder and then sandwiched between two cover glasses (25×80 mm, thickness 1.5 mm) and dipped in a water bucket. Irradiation was carried out with a 400-W high-pressure mercury lamp for 24 h. Dimers **5** were separated from intramolecular cyclization products by preparative GPC runs. Isomeric products **2** and **3** were separated by preparative HPLC runs.

References: S. Kohmoto, T. Kobayashi, T. Nishio, I. Iida, K. Kishikawa, M. Yamamoto, K. Yamada, *J. Chem. Soc., Perkin Trans. 1*, 529 (1996).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *cis*-9-decalyl aryl ketone, Norrish type II photochemistry, cyclopropanol, cyclobutanol, cyclopentanol

**Experimental procedures:**

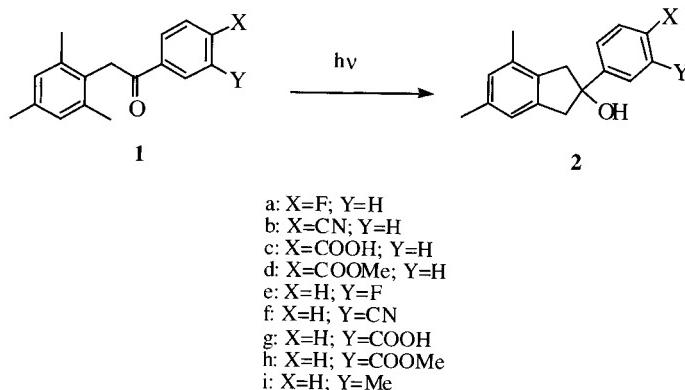
Irradiation of CH₃CN solutions of *cis*-9-decalyl *p*-carbomethoxyphenyl ketone **1** (145 mg) through Pyrex afforded cyclobutanols **2** (47%) and **5** (47%) along with 6% of cyclopentanone **4**. In contrast, when crystals of ketone **1** were irradiated (Pyrex, -20 °C, 76 mg), a mixture of cyclobutanol **2** (81%) and cyclopropanol **3** (19%) was formed.

References: E. Cheung, T. Kang, J.R. Scheffer, J. Trotter, *Chem. Commun.*, 2309 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *a*-mesitylacetophenone, photocyclization, 2-indanol



Experimental procedures:

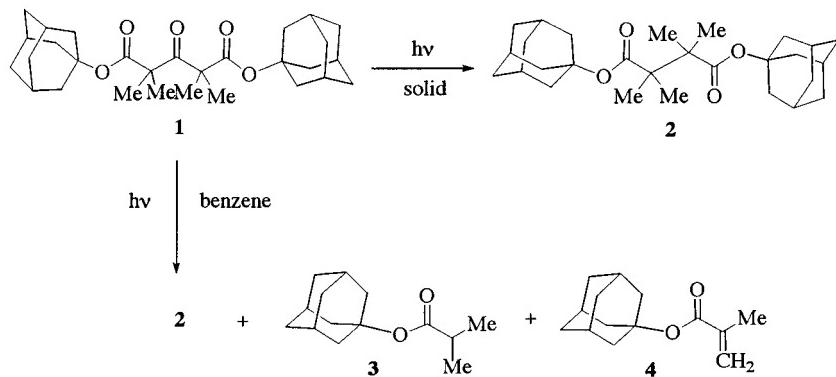
5–10 mg samples were placed between two Pyrex microscope slides, and by sliding the top and bottom plates back and forth, the sample was distributed over the surface in a thin, even layer. The microscope plates were Scotch-taped together at the top and bottom ends, place in a polyethylene bag, and thoroughly degassed with nitrogen. The bag was then sealed under a positive pressure of nitrogen with a heat-sealing device and placed 5 cm from the immersion well. Workup of the solid-state photolysis samples consisted of washing the solid off the plate with ether into a suitable container and determining the conversion by gas chromatography.

References: E. Cheung, K. Rademacher, J.R. Scheffer, J. Trotter, *Tetrahedron*, **56**, 6739 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 1,1,3,3-tetramethyl diadamantyl-1,3-acetonedicarboxylate, decarbonylation, photoirradiation

**Experimental procedures:**

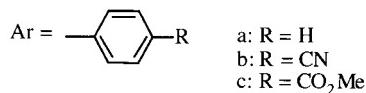
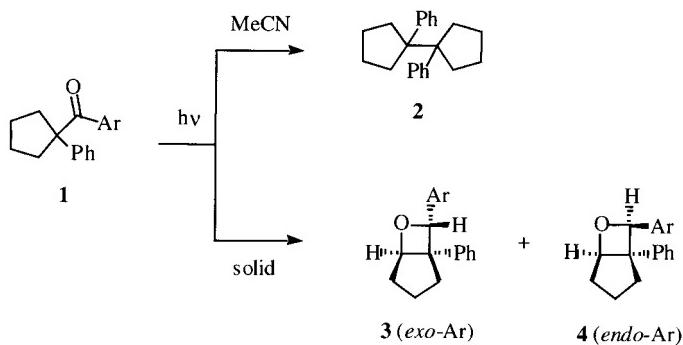
Finely powdered solid samples of ketodiester **1** (5 mg) were placed evenly between two microscope slides (which also acted as a $\lambda > 305$ nm filter) and placed at a similar distance from a medium-pressure Hg Hanovia lamp. After 4 h of irradiation, compound **2** was obtained in 87% yield.

References: Z. Yang, D. Ng, M. A. Garcia-Garibay, *J. Org. Chem.*, **66**, 4468 (2001); Z. Yang, M. A. Garcia-Garibay, *Org. Lett.*, **2**, 1963 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 1-phenylcyclopentyl ketone, Paterno-Buchi reaction, Norrish type I photoreaction, oxetane



Experimental procedures:

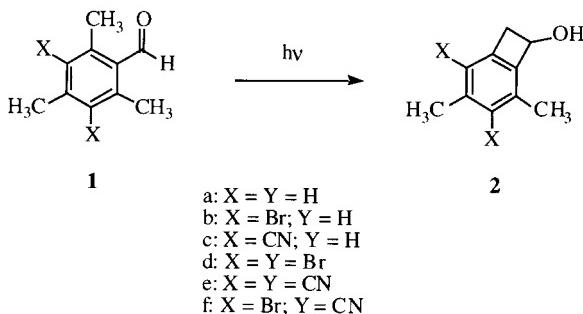
Solid-state photolysis was performed using a 450-W hanovia medium-pressure mercury lamp fitted with a Pyrex filter ($\lambda > 290$ nm). The crystalline **1a** was irradiated for 22.5 h at -20°C to give a mixture of *exo*-isomer **3a** and *endo*-isomer **4a** in 63 and 12% yield, respectively.

References: T. Kang, J.R. Scheffer, *Org. Lett.*, **3**, 3361 (2001).

Type of reaction: C–C bond formation

Reaction condition: solid state

Keywords: *o*-alkyl aromatic aldehyde, photocyclization, benzocyclobutanol

**Experimental procedures:**

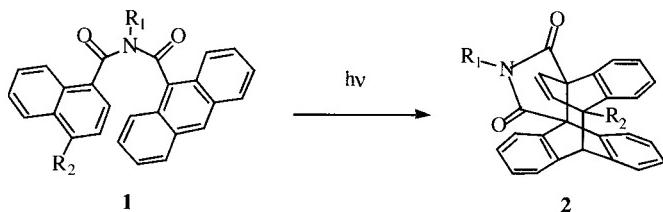
In a typical reaction, ca. 100 mg of the gently ground aldehyde was dispersed in a Pyrex container and purged with a stream of nitrogen gas for 15–10 min. The solid sample was subsequently irradiated, under a nitrogen gas atmosphere, in a Rayonet reactor fitted with 350 nm lamps for 24 h. After this period, the irradiated mixture was subjected to silica gel column chromatography. The combined fractions from the chromatography corresponding to the cyclobutanol were stripped off the solvent in vacuo at room temperature and characterized.

References: J.N. Moorthy, P. Mal, R. Natarajan, P. Venugopalan, *J. Org. Chem.*, **66**, 7013 (2001).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 9-anthryl-*N*-(naphthylcarbonyl)carboxamide, [4+4]photocycloaddition



- a: $R_1=C_6H_5CH_2$; $R_2=H$
 b: $R_1=o-CH_3C_6H_4CH_2$; $R_2=H$
 c: $R_1=p-CH_3C_6H_4CH_2$; $R_2=H$
 d: $R_1=o-FC_6H_4CH_2$; $R_2=H$
 e: $R_1=o-(CH_3)_3CC_6H_4$; $R_2=H$
 f: $R_1=n-C_3H_7$; $R_2=H$
 g: $R_1=i-C_3H_7$; $R_2=CH_3$

Experimental procedures:

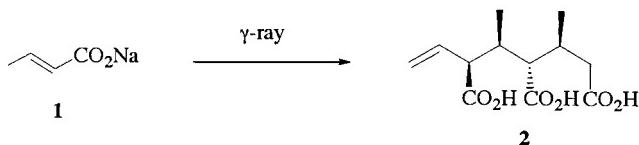
Powdered single crystals of **1** (ca. 20 mg) were sandwiched between two Pyrex cover glasses and placed in a polyethylene bag, which was irradiated with a 400-W high-pressure mercury lamp for 6 h (3 h for each side of the sample) in an ice-water bath. Out of seven carboxamides examined, **1a**, **1e** and **1g** showed intramolecular photocycloaddition in solid state to give the [4+4] cycloadducts **2a**, **2e**, and **2g** in an almost quantitative yield after complete conversion, and **1f** gave **2f** in 9% yield.

References: S. Kohmoto, Y. Ono, H. Masu, K. Yamaguchi, K. Kishikawa, M. Yamamoto, *Org. Lett.*, **3**, 4153 (2001).

Type of reaction: C–C bond formation

Reaction condition: solid state

Keywords: sodium *trans*-2-butenoate, trimerization, γ -ray irradiation, tricarboxylic acid



Experimental procedures:

1 (3.24 g, 29.9 mmol) was irradiated (15.6 Mrad) in a Gammacell 220 Irradiation Chamber (Atomic Energy of Canada, Ltd.), equipped with a ^{60}Co source (nominal activity as of June 1990, 0.049 Mrad h^{-1}). The resulting colorless powder

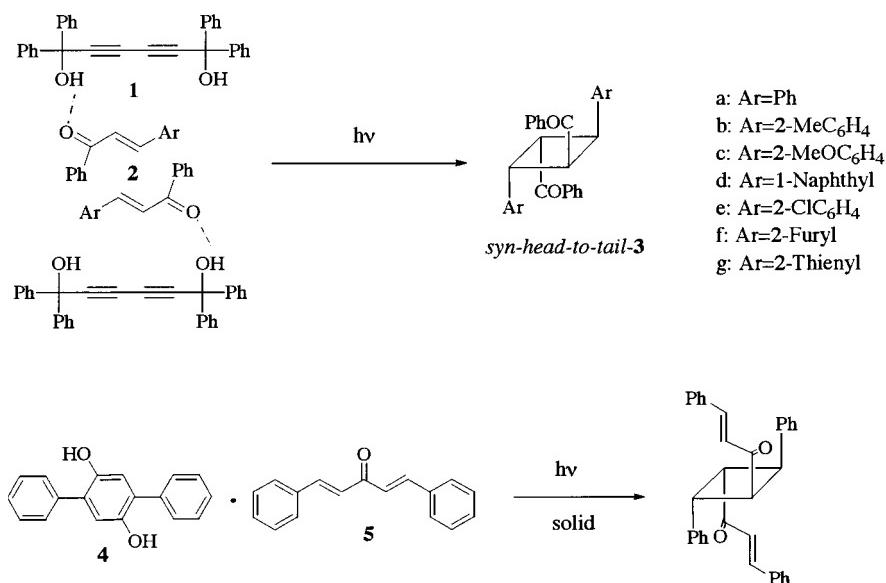
was dissolved in H₂O (20 mL) to give a homogeneous solution which was acidified with conc. HCl (3.5 mL). The colorless precipitate that formed was isolated by filtration and dried in vacuo (0.25 Torr) over anhydrous CaSO₄ to give **2** (colorless powder, 1.4 g, 55%).

References: G. C. D. Delgado, K. A. Wheeler, B. B. Snider, B. M. Foxman, *Angew. Chem. Int. Ed. Engl.*, **30**, 420 (1991).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: chalcone, dibenzylidene acetone, inclusion crystal, [2+2]photocycloaddition, cyclobutane



Experimental procedures:

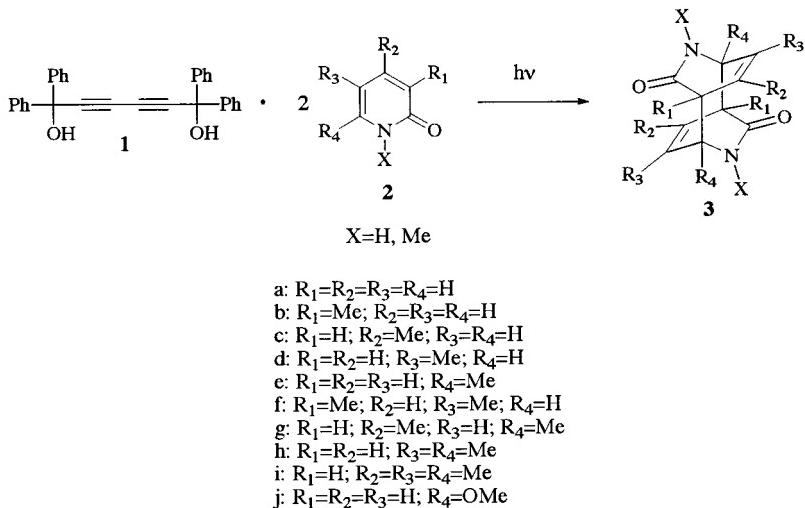
Irradiation of powdered 1:2 inclusion complex of **1** and chalcone **2** by a high-pressure Hg-lamp at room temperature for 1 h gave a single photoaddition product *syn*-head-to-tail dimer **3a** in 82% yield.

References: K. Tanaka, F. Toda, *Chem. Commun.*, 593 (1983); M. Kaftory, K. Tanaka, F. Toda, *J. Org. Chem.*, **50**, 2154 (1985).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 2-pyridone, inclusion complex, [4+4]photocycloaddition



Experimental procedures:

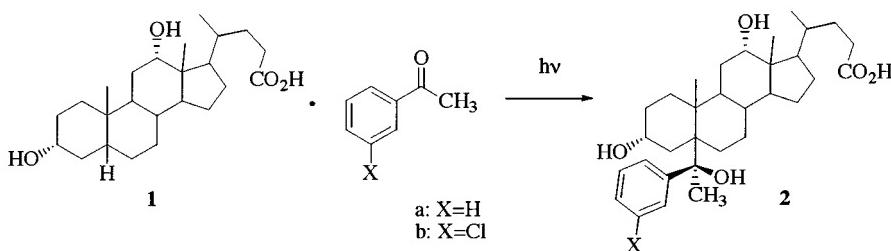
A powdered 1:2 inclusion complex of **1** and **2** was irradiated by 400-W high-pressure Hg-lamp for 6 h at room temperature. The reaction mixture was recrystallized from MeOH to give [4+4] dimer **3**.

References: K. Tanaka, F. Toda, *Nippon Kagakukaishi*, 141 (1984); M. Kuzuya, A. Noguchi, N. Yokota, T. Okuda, F. Toda, K. Tanaka, *Nippon Kagakukaishi*, 1746 (1986).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: deoxycholic acid, acetophenone, host-guest complex, photoirradiation



Experimental procedures:

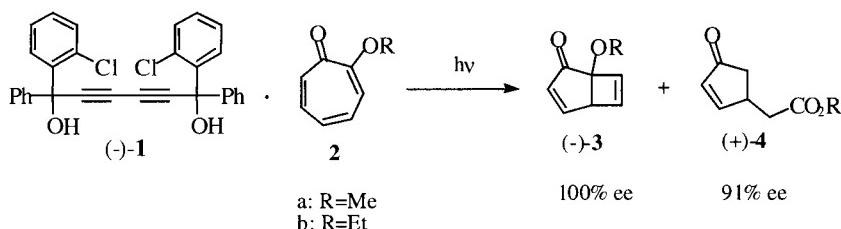
In a typical experiment, 1–2 g of complex was irradiated at room temperature through Pyrex dishes, $\lambda > 300$ nm, for about 30 days. The crystals were generally in the form of powder. Single crystals preserved their integrity during irradiation. The products were separated by chromatography on silica gel 1 : 100 (eluted with $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{AcOH}$ in a ratio of 90.5 : 5.0 : 0.5) and by preparative TLC with the same eluent in a ratio of 90.5 : 9.0 : 0.5 by using UV detection and phosphomolybdic acid as coloring spray.

References: C. P. Tang, H. C. Chang, R. Popovitz-Biro, F. Frolow, M. Lahav, L. Leiserowitz, R. K. McMullan, *J. Am. Chem. Soc.*, **107**, 4058 (1985).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: tropolone alkyl ether, inclusion crystal, [2+24]photocycloaddition

**Experimental procedures:**

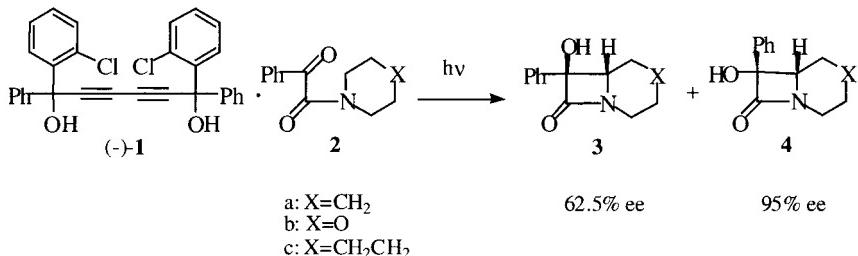
Irradiation of powdered 1:1 inclusion complex of **(-)-1** and **2a** by a high-pressure Hg-lamp at room temperature for 72 h (50% conversion) gave **(-)-3a** (11% yield, $[\alpha]_D^{25} -168^\circ$ c 0.2, CH_3OH , 100% ee) and **(+)-4a** (26% yield, $[\alpha]_D^{25} -89.5^\circ$ (c 0.2, CH_3OH , 91% ee).

References: F. Toda, K. Tanaka, *Chem. Commun.*, 1429 (1986).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: α -oxoamide, inclusion crystal, Norrish type II photoreaction, β -lactam

**Experimental procedures:**

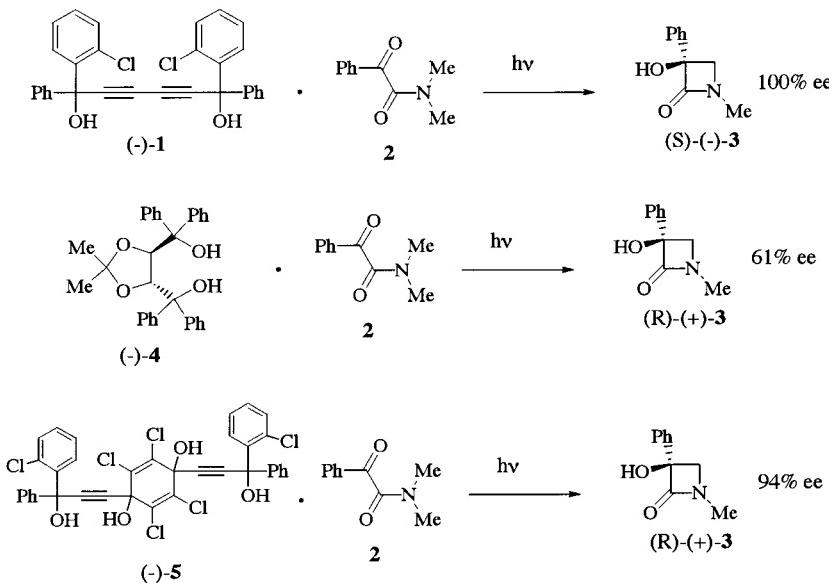
Photoirradiation of a 1:1 inclusion complex of (-)-1 and **2a** by high-pressure Hg-lamp for 100 h at room temperature gave optically active β -lactams (-)-**3a** of 62.5% ee and (-)-**4a** of 95% ee in 38 and 29% yields, respectively.

References: F. Toda, K. Tanaka, M. Yagi, *Tetrahedron*, **43**, 1495 (1987).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: α -oxoamide, inclusion complex, Norrish type II photoreaction, β -lactam



Experimental procedures:

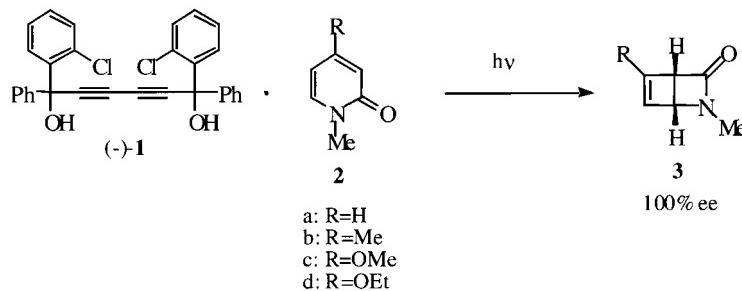
The powdered 1:1 complex (0.85 g) of (*-*)-**1** and **2** was irradiated by a 400-W high-pressure Hg lamp at room temperature, for 27 h with occasional grinding with a pestle and mortar. The reaction mixture was chromatographed on silica gel with benzene-ethyl acetate as solvent to give (*-*)-**1** (1.0 g, 100%) and 100% ee (*-*)-**3**, $[\alpha]_D$ –99.7° (*c* 0.34, CHCl₃) as colorless plates, mp 123–124°C.

References: M. Kaftory, M. Yagi, K. Tanaka, F. Toda, *J. Org. Chem.*, **53**, 4391 (1988); F. Toda, H. Miyamoto, K. Kanemoto, *Chem. Commun.*, 1719 (1995); F. Toda, H. Miyamoto, M. Inoue, S. Yasaka, I. Matijasic, *J. Org. Chem.*, **65**, 2728 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 2-pyridone, inclusion crystal, [2+2]photodimerization, β -lactam

**Experimental procedures:**

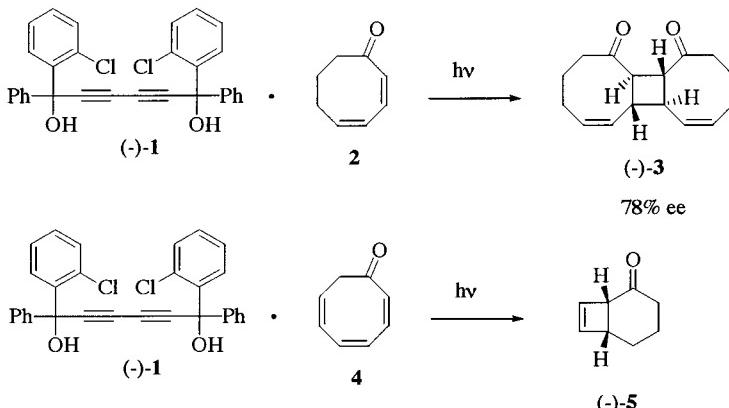
A powdered 1:1 inclusion complex of (*-*)-**1** and 4-methoxy-1-methylpyridone **2c** was irradiated by 100-W high-pressure Hg-lamp at room temperature in the solid state. The crude reaction product was chromatographed on silica gel using CHCl₃ as a solvent to give a mixture of host compound and **3**, from which **3** was isolated by distillation as an oil ($[\alpha]_D$ –123° (*c* 0.026, CHCl₃), 100% ee).

References: F. Toda, K. Tanaka, *Tetrahedron Lett.*, **29**, 4299 (1988).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: cycloocta-2,4,6-trien-1-one, cycloocta-2,4-dien-1-one, inclusion complex, [2+2]photocycloaddition, cyclobutane



Experimental procedures:

Irradiation of finely powdered 3:2 complex of **(-)-1** and **2** (2 g) in the solid state for 48 h gave a crude reaction product. Purification of the crude product by column chromatography on silica gel using CHCl_3 as solvent gave **(-)-3**, which on distillation gave pure **(-)-3** of 78% ee (0.16 g, 55%, bp $200^\circ\text{C}/1\text{ mmHg}$, $[\alpha]_D -34.7^\circ$ (*c* 0.11, CHCl_3)).

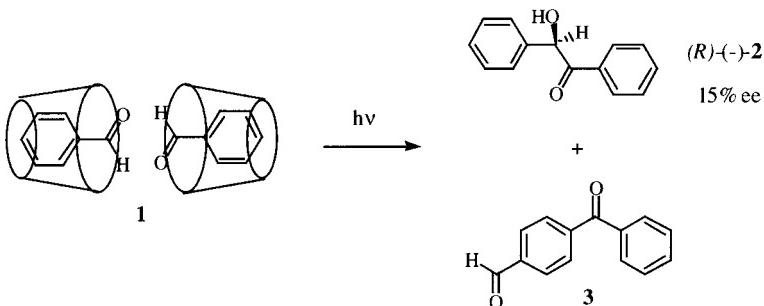
Irradiation of finely powdered 1:2 complex of **(-)-1** and **4** (1.1 g) in the solid state for 168 h gave a crude reaction product. Purification of the crude product by column chromatography on silica gel using CHCl_3 as solvent gave **(-)-5**, which on distillation gave pure **(-)-5** (0.052 g, 14%, bp $200^\circ\text{C}/1\text{ mmHg}$, $[\alpha]_D -62.9^\circ$ (*c* 0.12, CHCl_3)).

References: F. Toda, K. Tanaka, M. Oda, *Tetrahedron*, **29**, 653 (1988); T. Fujiwara, N. Nanba, K. Hamada, F. Toda, K. Tanaka, *J. Org. Chem.*, **55**, 4532 (1990).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: β -cyclodextrin, benzaldehyde, asymmetric synthesis, photoirradiation, benzoin, 4-benzoylbenzaldehyde



Experimental procedures:

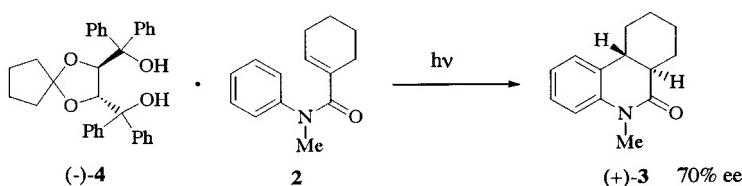
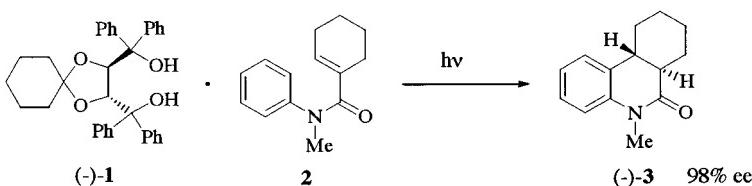
Photolyses of the solid cyclodextrin complexes **1** were carried out with a Hanovia 450-W medium-pressure Hg lamp for 3 h at room temperature in a quartz vessel under vacuum. The photolysis vessel was tumbled continuously during the irradiation to ensure homogeneous photolysis of the sample. Conversions were limited to less than 20%. After photolysis, the solid complexes were dissolved in excess water and extracted with diethyl ether and chromatographed with hexane-ethyl acetate (5:1) to isolate the products in pure form. Irradiation of solid β -cyclodextrin complexes of benzaldehyde resulted in an intramolecular reaction to give benzoin (*R*)-(–)-**2** and 4-benzoylbenzaldehyde **3** (7:3, 80%).

References: V.P. Rao, N.J. Turro, *Tetrahedron Lett.*, **30**, 4641 (1989).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *N*-methyl cyclohex-1-enylanilide, inclusion crystal, [2+2]photocyclo-addition, 3,4-dihydroquinolin-2(1*H*)-one



Experimental procedures:

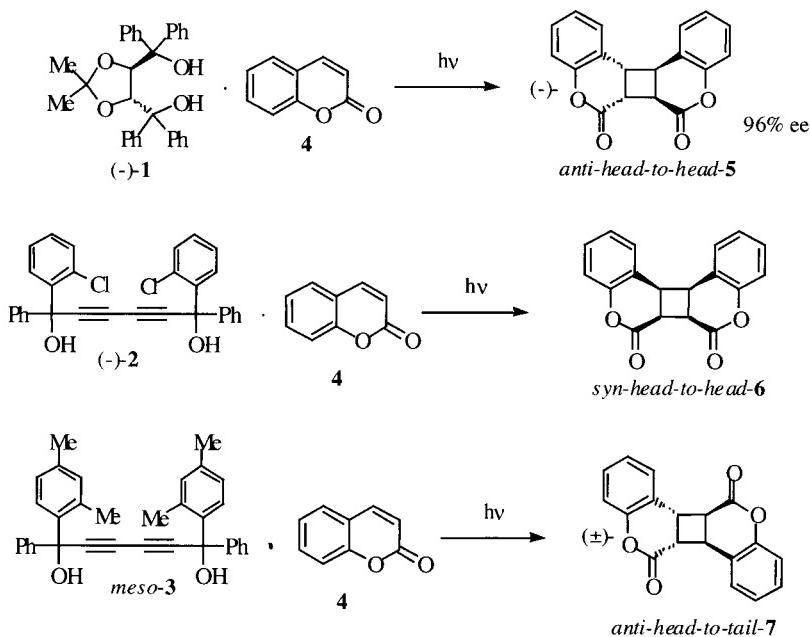
Photoirradiation of a suspension of powdered 1:1 complex of (−)-**1** and **2** (3.2 g) in water (150 mL) containing a small amount of sodium alkyl sulfate as a surfactant was carried out for 50 h using a 100-W high-pressure Hg lamp under stirring. The reaction product was filtered, air dried, and chromatographed on silica gel using CH₂Cl₂ as an eluent to give (−)-*trans*-**3** (0.67 g, 70% yield, mp 123–125 °C, [α]_D−177° (*c* 0.5 CH₃OH), 98% ee).

References: K. Tanaka, O. Kakinoki, F. Toda, *Chem. Commun.*, 1053 (1992); S. Ohba, H. Hosomi, K. Tanaka, H. Miyamoto, F. Toda, *Bull. Chem. Soc. Jpn.*, **73**, 2075 (2000); H. Hosomi, S. Ohba, K. Tanaka, F. Toda, *J. Am. Chem. Soc.*, **122**, 1818 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: coumarin, inclusion crystal, [2+2]photodimerization, cyclobutane

**Experimental procedures:**

Recrystallization of (−)-**1** (10.0 g, 21.5 mmol) and **4** (3.2 g, 21.9 mmol) from AcOEt (20 mL)-hexane (100 mL) gave the 1:1 inclusion crystal as colorless needles (5.7 g, 43%, mp 95–98 °C). Irradiation of the powdered 1:1 complex (1 g)

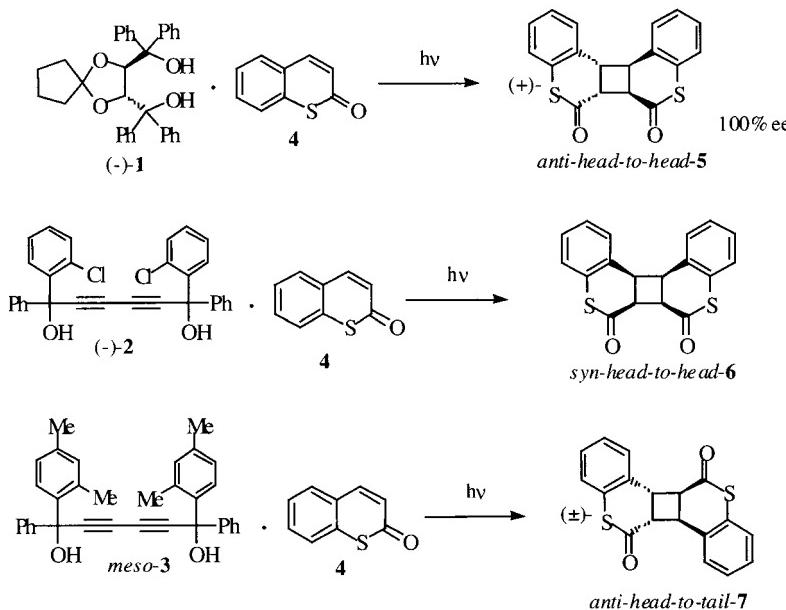
in water (100 mL) containing surfactant for 3 h gave a 2:1 complex of (−)-**1** and (−)-**5** of 96% ee as colorless needles (0.96 g, 96%, mp 228–232 °C).

References: K. Tanaka, F. Toda, *J. Chem. Soc., Perkin Trans. 1*, 943 (1992); K. Tanaka, F. Toda, E. Mochizuki, N. Yasui, Y. Kai, I. Miyahara, K. Hirotsu, *Angew. Chem. Int. Ed. Engl.*, **38**, 3523 (1999); K. Tanaka, F. Toda, E. Mochizuki, N. Yasui, Y. Kai, I. Miyahara, K. Hirotsu, *Tetrahedron*, **56**, 6853 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: thiocoumarin, inclusion crystal, [2+2]photodimerization, cyclobutane



Experimental procedures:

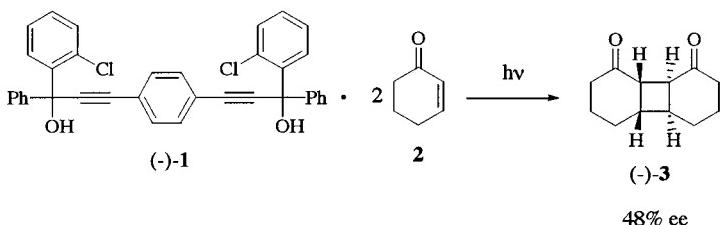
When a mixture of thiocoumarin **4** and optically active host compound *(R,R)*-(−)-**1** in butyl ether was kept at room temperature for 12 h, a 1:1 inclusion complex (mp 106–108 °C) was obtained as colorless needles. The 1:1 complex gave *anti-head-to-head* dimer (+)-**5** (mp 254–255 °C) of 100% ee ($[\alpha]_D +182^\circ$, c 0.02 in CHCl_3) in 73% yield upon photoirradiation in the solid state. The optical purity of **5** was determined by HPLC on the chiral stational phase Chiralpak AS with using hexane-EtOH (95:5) as an eluent.

References: K. Tanaka, F. Toda, *Mol. Cryst. Liq. Cryst.*, **313**, 179 (1998); K. Tanaka, F. Toda, E. Mochizuki, N. Yasui, Y. Kai, I. Miyahara, K. Hirotsu, *Tetrahedron*, **56**, 6853 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: cyclohex-2-enone, inclusion crystal, [2+2]photodimerization, cyclobutane



Experimental procedures:

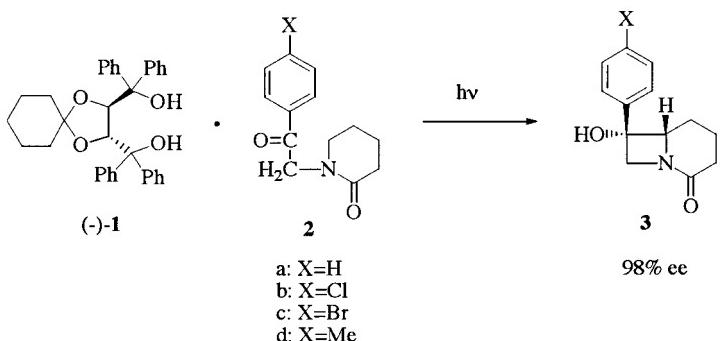
A solution of **(-)-1** (5.0 g, 8.94 mmol) and **2** (1.72 g, 17.9 mmol) in ether-hexane (1:1, 10 mL) was kept at room temperature for 6 h to give a 1:2 complex of **(-)-1** and **2** as colorless prisms (6.1 g, 91%), mp 90–95 °C. A suspension of the powdered complex (4.2 g) in water (100 mL) containing a small amount of sodium alkylsulfate as surfactant was irradiated at room temperature for 24 h. The reaction mixture was filtered, dried, and distilled in vacuo to give **(-)-3** in 48% ee as an oil (0.8 g, 74.8%, $[a]_D$ –61.0° (*c* 0.4, MeOH)).

References: K. Tanaka, O. Kakinoki, F. Toda, *J. Chem. Soc., Perkin Trans. I*, 307 (1992); K. Tanaka, H. Mizutani, I. Miyahara, K. Hirotsu, F. Toda, *Cryst. Eng. Comm.*, 3 (1999).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *N*-(aryloylmethyl)- δ -valerolactam, inclusion complex, photocyclization, azetidine



Experimental procedures:

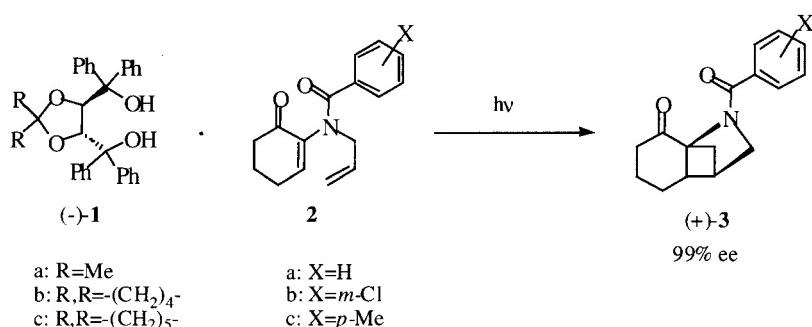
A suspension of the powdered 1:1 inclusion compound of (*-*)-**1** and **2a** (3.21 g) in water (120 mL) containing sodium alkylsulfate as a surfactant was irradiated for 12 h while being stirred at room temperature. The reaction mixture was filtered to give crude crystals and an aqueous solution. The crude crystals were purified by column chromatography on silica gel followed by recrystallization from AcOEt to give (+)-**3a** of 98% ee (0.42 g, 59% yield) and recovered (*-*)-**1** (0.24 g, 25% yield).

References: F. Toda, K. Tanaka, O. Kakinoki, T. Kawakami, *J. Org. Chem.*, **58**, 3783 (1993); D. Hashizume, Y. Ohashi, K. Tanaka, F. Toda, *Bull. Chem. Soc. Jpn.*, **67**, 2383 (1994).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 2-[*N*-(2-propenyl)amino]cyclohex-2-enone, inclusion complex, photo-cyclization

**Experimental procedures:**

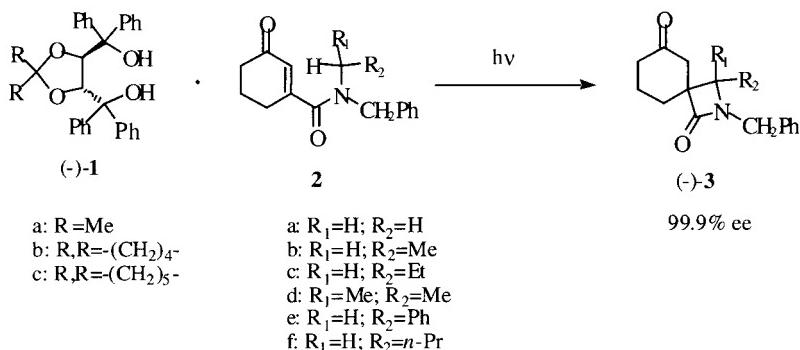
A suspension of powdered 2:1 inclusion complex of (*-*)-**1a** and **2a** (1.2 g, 0.97 mmol) in water (120 mL) containing alkylsulfate (0.1 g) as a surfactant was irradiated under stirring for 17 h. The reaction product was filtered, dried and chromatographed on silica gel using AcOEt-hexane (1:1) as an eluent to give (+)-**3a** (0.16 g, 0.62 mmol, 64% yield, $[\alpha]_D +70^\circ$ (*c* 1.0, CCl₄), mp 106–107 °C).

References: F. Toda, H. Miyamoto, K. Takeda, R. Matsugawa, N. Maruyama, *J. Org. Chem.*, **58**, 6208 (1993).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 3-oxo-2-cyclohexenecarboxamide, inclusion complex, photocyclization, spiro compound



Experimental procedures:

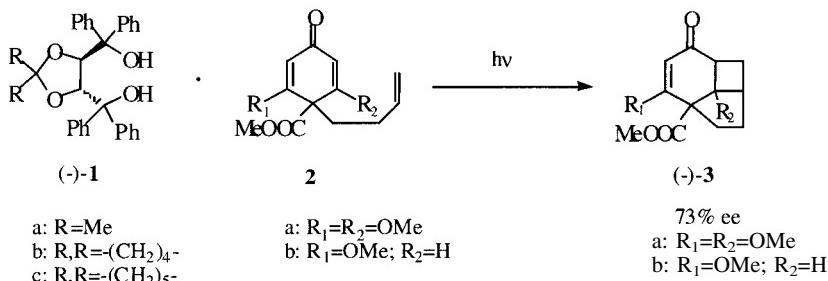
A suspension of powdered 2:1 inclusion complex of **(-)-1b** and **2b** (6.72 g, 5.29 mmol) in water (120 mL) containing alkylsulfate (0.1 g) as a surfactant was irradiated under stirring for 4 h. The reaction product was filtered, dried and chromatographed on silica gel using AcOEt-hexane (1:1) as an eluent to give **(-)-3b** (1.18 g, 87% yield).

References: F. Toda, H. Miyamoto, K. Takeda, R. Matsugawa, N. Maruyama, *J. Org. Chem.*, **58**, 6208 (1993).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 4-(3-butenyl)cyclohexa-2,5-dien-1-one, inclusion complex, photocyclization



Experimental procedures:

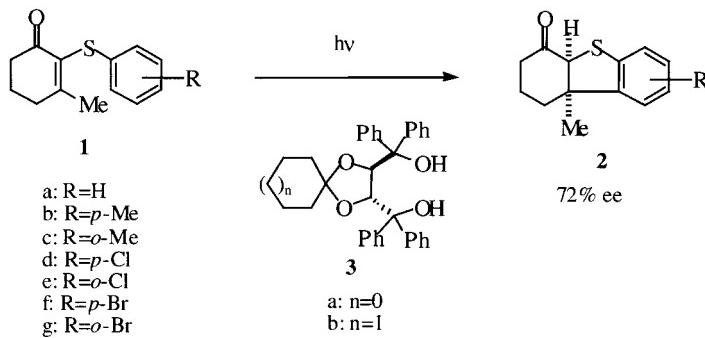
A suspension of powdered 2:1 inclusion complex of **(-)-1a** and **2a** (0.36 g) in water (100 mL) containing alkylsulfate (0.1 g) as a surfactant was irradiated under stirring for 5 h. The reaction product was filtered, dried and chromatographed on silica gel using AcOEt-hexane (1:1) as an eluent to give **(+)-3b** of 73% ee (0.04 g, 50% yield, $[a]_D^{25} +5.7^\circ$ CH₃OH, mp 110–113 °C).

References: F. Toda, H. Miyamoto, K. Takeda, R. Matsugawa, N. Maruyama, *J. Org. Chem.*, **58**, 6208 (1993).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 2-arylthio-3-methylcyclohex-2-en-1-one, inclusion complex, photocyclization, thiolane



Experimental procedures:

When a benzene-hexane solution of **(-)-3b** (1.09 g, 2.15 mmol) and **1c** (0.5 g, 2.15 mmol) was left at room temperature for 24 h, a 1:1 inclusion compound of **(-)-3b** and **1c** was obtained as colorless crystals (1.51 g, 95%). Irradiation of the

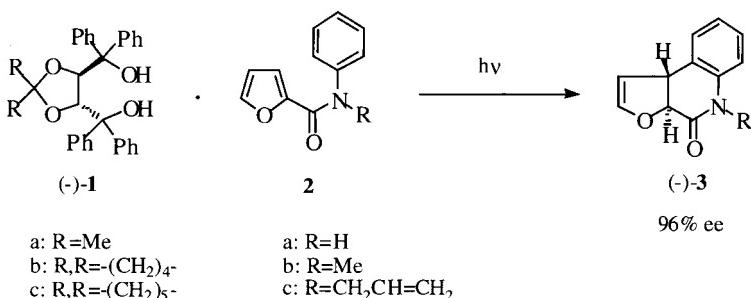
inclusion compound (1.22 g) with stirring for 30 h in water (200 mL) containing hexadecyltrimethylammonium bromide (0.1 g) gave a crude reaction product. This was filtered, air dried and distilled at 250 °C (2 mmHg) to give (+)-**2c** of 72% ee (0.33 g, 86% yield).

References: F. Toda, H. Miyamoto, S. Kikuchi, R. Kuroda, F. Nagami, *J. Am. Chem. Soc.*, **118**, 11315 (1996).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *N*-alkylfuran-2-carboxanilide, inclusion complex, photocyclization, lactam



Experimental procedures:

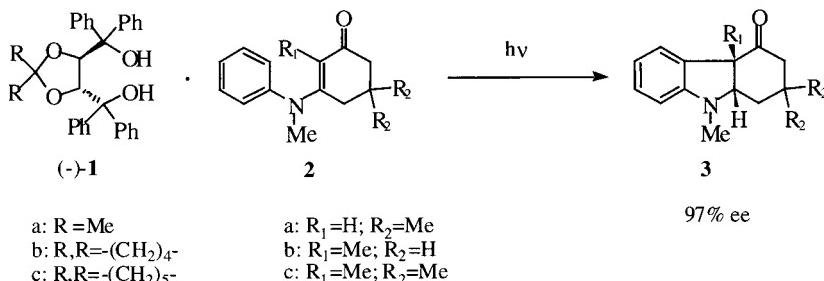
Photoirradiation of a suspension of powdered 1:1 complex of (-)-**1b** and **2c** (1.4 g) in water (80 mL) containing hexadecyltrimethylammonium bromide (0.2 g) as a surfactant was carried out at room temperature for 77 h under stirring. The reaction product was filtered, air-dried, and chromatographed on silica gel using toluene-AcOEt (10:1) as an eluent to afford (-)-*trans*-photocyclization product **3c** of 96% ee (0.22 g, 50% yield, mp 102–104 °C, $[a]_D$ –289° (*c* 0.5, MeOH).

References: F. Toda, H. Miyamoto, K. Kanemoto, *J. Org. Chem.*, **61**, 6490 (1996).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *N*-phenyl enaminone, inclusion complex, photocyclization, dihydroindole derivative



Experimental procedures:

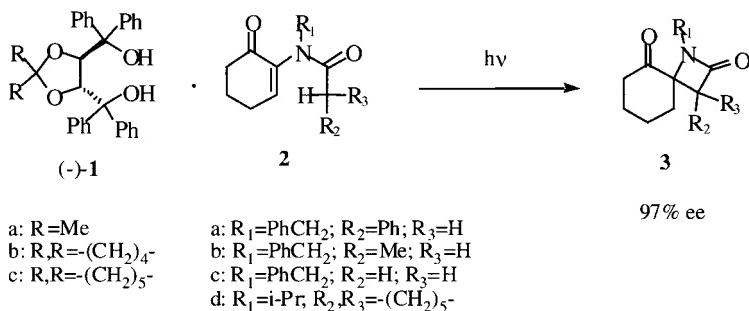
A suspension of powdered 1:1 inclusion complex of **(-)-1a** and **2a** (3.07 g, 4.41 mmol) in water (120 mL) containing hexadecyltrimethylammonium bromide (0.1 g) as a surfactant was irradiated under stirring for 16 h with 100-W high-pressure Hg-lamp. The reaction mixture was filtered, dried and chromatographed on silica gel using AcOEt-toluene (1:9) as an eluent to give **(+)-3a** of 97% ee after distillation at 180 °C/2 mmHg as colorless oil.

References: F. Toda, H. Miyamoto, T. Tamashima, M. Kondo, Y. Ohashi, *J. Org. Chem.*, **64**, 2690 (1999).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: cyclohexenone, inclusion complex, photocyclization, β -lactam, spiro compound



Experimental procedures:

A suspension of a powdered 1:1 inclusion compound of **(-)-1c** and **2a** (2.6 g, 3.2 mmol) in water (120 mL) containing hexadecyltrimethylammonium bromide (0.04 g) as a surfactant was irradiated with stirring for 8 h. The reaction product was filtered, dried, and chromatographed on silica gel using AcOEt-hexane (1:4)

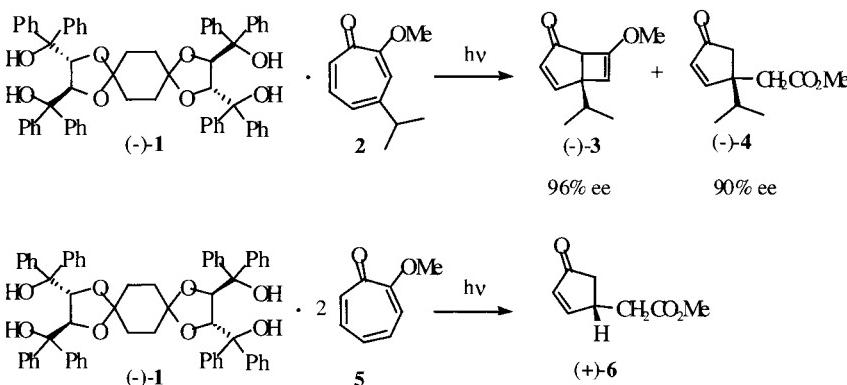
as the eluent to give **(−)-3a** in 97% ee as a colorless oil (0.27 g, 26% yield). $[\alpha]_D^{25} -48^\circ (c\ 0.6, \text{MeOH})$.

References: F. Toda, H. Miyamoto, M. Inoue, S. Yasaka, I. Matijasic, *J. Org. Chem.*, **65**, 2728 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 4-isopropyltropolone methyl ester, inclusion crystal, [2+2]photocycloaddition, bicyclo[3.2.0]hepta-3,6-dien-2-one, methyl-4-oxocyclopent-2-ene-1-acetate



Experimental procedures:

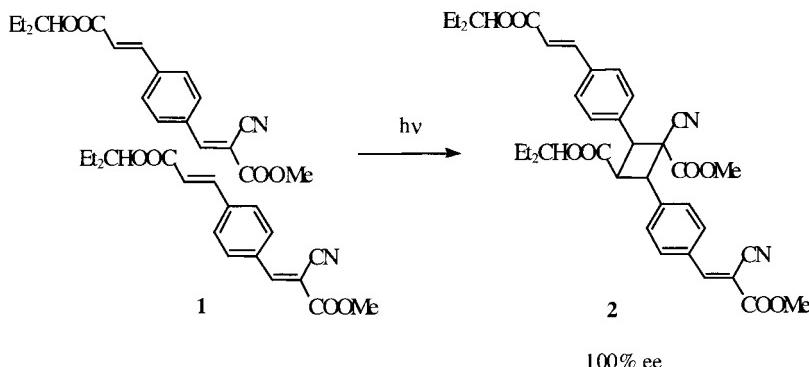
A crystalline powder of the 2:1:1 complex of **(-)-1**, **2** and CHCl_3 (4.44 g) was irradiated by a 400-W high-pressure Hg-lamp (Pyrex filter) in the solid state for 70 h. Separation of the reaction mixture by silica gel column chromatography gave a mixture of **(-)-3** (96% ee) and **(-)-4** (90% ee). The optical purities were determined by HPLC (Chiralcel OD, Daicel).

References: K. Tanaka, R. Nagahiro, Z. Lipkowska, *Org. Lett.*, **3**, 1567 (2001).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: [2+2]photodimerization, absolute asymmetric synthesis, cyclobutane

**Experimental procedures:**

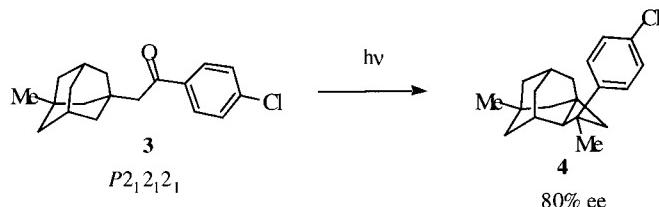
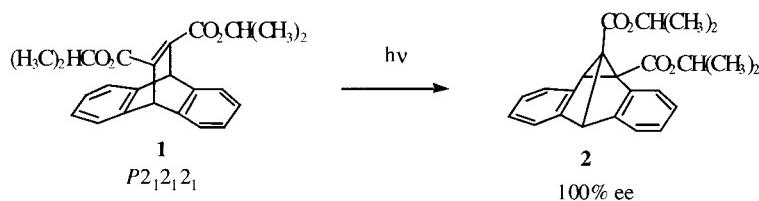
Achiral **1** crystallizes from EtOH-CH₂Cl₂ in a chiral structure of space group *P*2₁. The monomer was suspended in a mixture of methanol-water (10%) and irradiated under continuous stirring with a 450-W immersion high-pressure Hano-via Hg-lamp at -2 °C for periods of 20–60 h. Dimer **2**: mp (racemic dimer) 170 °C; [α]_D 114° (100% ee).

References: L. Addadi, J. v. M. Lahav, *J. Am. Chem. Soc.*, **104**, 3422 (1982).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: di- π -methane and Norrish type II photorearrangement, chiral crystal



Experimental procedures:

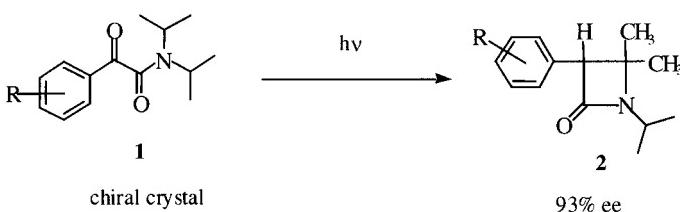
Large (20–85 mg) single crystals of diester **1** were grown by slow evaporation and were photolyzed by the output from a Molelectron UV-22 nitrogen laser (337 nm, 330 mW). The optical activity produced in each photolysis was determined by dissolving the sample in chloroform and measuring its $[\alpha]_D$ values.

References: S. V. Evance, M. G. Garibay, N. Omkaram, J. R. Scheffer, J. Trotter, F. Wiersko, *J. Am. Chem. Soc.*, **108**, 5648 (1986).

Type of reaction: C=C bond formation

Reaction condition: solid-state

Keywords: oxoamide, chiral crystal, Norrish type II photoreaction, β -lactam



- | | | | |
|-----------|-----------|-----------|--------------------------|
| a: R=H | e: R=p-Me | h: R=o-Me | k: R=3,5-Me ₂ |
| b: R=m-Me | f: R=p-Cl | i: R=o-Cl | l: R=3,4-Me ₂ |
| c: R=m-Cl | g: R=p-Br | j: R=o-Br | |
| d: R=m-Br | | | |

Experimental procedures:

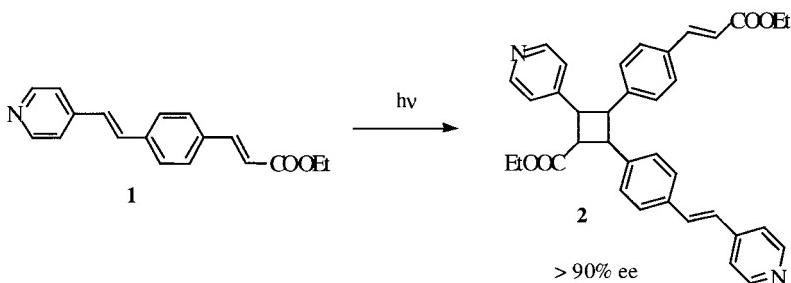
The powdered crystals of (+)-**1** (1 g) were irradiated with the Hg-lamp. The photoproduct (+)-**2**, after purification by column chromatography, received 93% enantiomeric excess, 74% chemical yield (0.74 g), $[a]_D +123^\circ$ (*c* 0.5, CHCl₃), and mp 149–150°C.

References: F. Toda, M. Yagi, S. Soda, *Chem. Commun.*, 1413 (1987); A. Sekine, K. Hori, Y. Ohashi, M. Yagi, F. Toda, *J. Am. Chem. Soc.*, **111**, 697 (1989); D. Hashizume, H. Kogo, A. Sekine, Y. Ohashi, H. Miyamoto, F. Toda, *J. Chem. Soc., Perkin Trans. 2*, 61 (1996).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 4-[2-(4-pyridyl)ethenyl]cinnamate, chiral crystal, [2+2]photodimerization, cyclobutane



Experimental procedures:

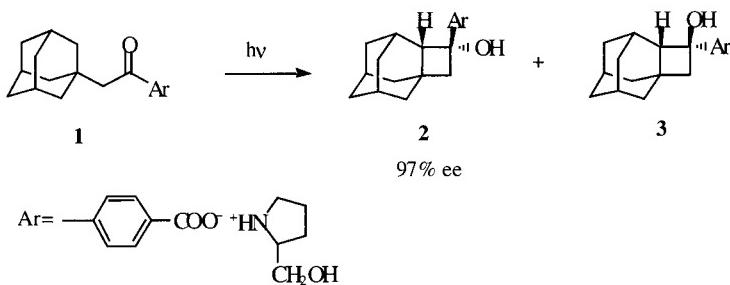
Finely powdered monomer crystals were dispersed in distilled water containing a few drops of surfactant and irradiated, with vigorous stirring, by a 500-W super-high-pressure mercury lamp set outside of the flask. Optically active **2** was obtained by the irradiation of crystals **1** with $\lambda > 365$ nm, and by successive purification by preparative TLC.

References: C. Chung, M. Hasegawa, *J. Am. Chem. Soc.*, **113**, 7311 (1991).

Type of reaction: C=C bond formation

Reaction condition: solid-state

Keywords: α -adamantyl ketone, prolinol, Norrish type II photoreaction, fused cyclobutane



Experimental procedures:

The samples were prepared for solid state photolysis by crushing the crystals between two Pyrex plates and sliding the plates back and forth so as to distribute the crystals over the surface in a thin, even layer. The sample plates were then taped together at the top and bottom ends, placed in polyethylene bags, degassed with nitrogen and sealed under a positive pressure of nitrogen with a heat-sealing device. The bags were immersed in a cooling bath maintained at -40°C by

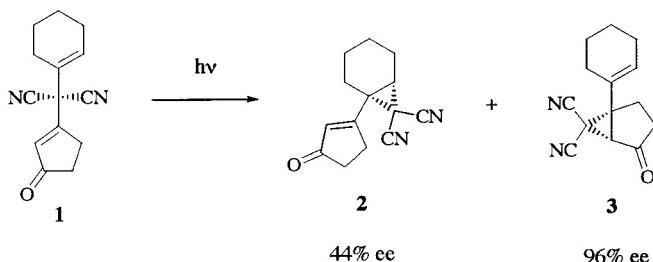
means of a cryomat and irradiated with the output from a 450-W Hanovia medium-pressure lamp. Conversions of 70% and higher were possible in the solid state runs without significant sample melting or loss of enantioselectivity. In a typical run, a “sandwich” containing 120 mg of salt required 24 h of photolysis.

References: R. Jones, J.R. Scheffer, J. Trotter, J. Yang, *Tetrahedron Lett.*, **33**, 5481 (1992).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: di- π -methane photorearrangement, chiral crystal, fused cyclopropane



Experimental procedures:

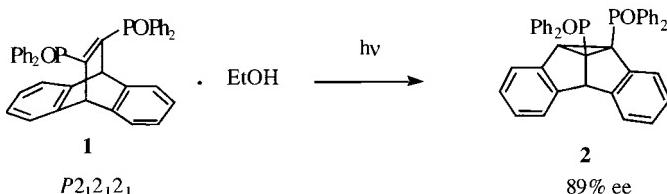
Crystalline **1** (6 g, 26.4 mmol) was ground to a fine powder and poured into a Pyrex vessel mounted in a Rayonet reactor ($\lambda=350\pm40$ nm) containing vigorously stirred H₂O (300 mL). A cooling finger was lowered into the mixture and the vessel was irradiated for 90 h. The turbid lightly orange mix was poured into a separatory funnel and the remaining orange and yellow solid/melt was washed from the vessel with CH₂Cl₂. Extractive workup afforded a dark reddish orange oil from which **1** (2.93 g, 49%), **2** (1.36 g, 23%) and **3** (1.68 g, 28%) were chromatographically isolated.

References: A.L. Roughton, M. Muneer, M. Demuth, *J. Am. Chem. Soc.*, **115**, 2085 (1993).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 9,10-dihydro-9,10-ethenoanthracene derivative, di- π -methane photorearrangement, chiral crystal, dibenzosemibullvalene

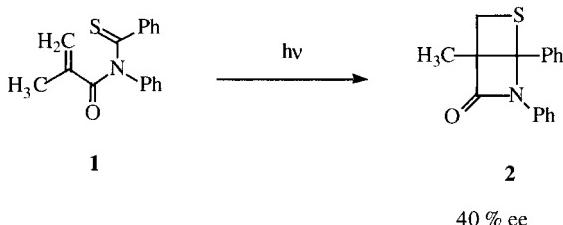
**Experimental procedures:**

Single crystals of the ethanol complex of **1** were irradiated through Pyrex and the chiral photoproduct **2** was tested for optical activity by polarimetry and chiral HPLC. This indicated an enantiomeric excess of 89% (84% conversion at room temperature).

References: T. Y. Fu, Z. Liu, J. R. Scheffer, J. Trotter, *J. Am. Chem. Soc.*, **115**, 12202 (1993).

Type of reaction: C–C bond formation**Reaction condition:** solid-state

Keywords: *N*-(thiobenzoyl)methacrylanilide, chiral crystal, photoirradiation, β -lactam

**Experimental procedures:**

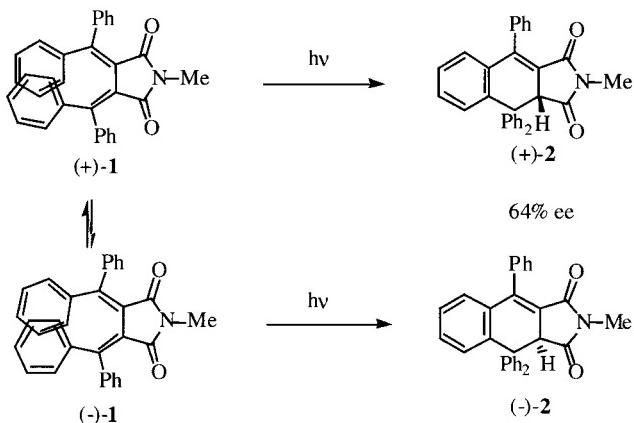
When powdered crystals of the monothioimide **1**, recrystallized from hexane, were irradiated under nitrogen through a Pyrex filter with the UV light from a 500-W high-pressure mercury lamp at 0°C for 12 h, a transformation occurred and the photoproduct was purified by column chromatography on silica gel; optically active $(+)$ -**2** was obtained in 75% yield, $[\alpha]_D^{25} +23^\circ$ (*c* 0.1, CHCl₃), 10% ee. The solid-state photoreaction proceeded even at -45°C, and optically active $(+)$ -**2** which showed a higher ee value was formed, $[\alpha]_D^{25} +93^\circ$ (*c* 0.1, CHCl₃), 40% ee (conv. 30%, yield 70%).

References: M. Sakamoto, N. Hokari, M. Takahashi, T. Fujita, S. Watanabe, I. Iida, T. Nishio, *J. Am. Chem. Soc.*, **115**, 818 (1993).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 3,4-bis(diphenylmethylen)-*N*-methylsuccimide, [4+2]photodimerization cyclization, 2-methyl-4,4,9-triphenyl-3*a*,4-dihydro-benz[f]isoindole-1,3-dione



Experimental procedures:

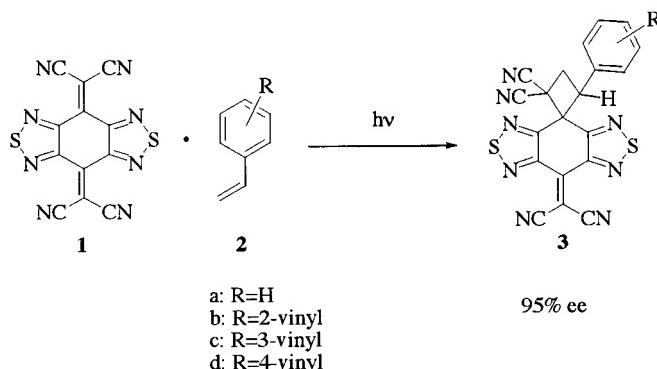
Photoirradiation of powdered (+)-**1** crystal (50 mg) by 100-W high-pressure Hg-lamp for 50 h gave (+)-**2** of 64% ee (50 mg, 100% yield, mp 285–287 °C, $[\alpha]_D +102^\circ$ (c 0.05, CHCl₃)). The optical purity was determined by HPLC on the chiral solid phase Chiralpak AS.

References: F. Toda, K. Tanaka, *Supramol. Chem.*, **3**, 87 (1994).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: styrene, charge-transfer complex, chiral crystal, [2+2]photocyclo-addition, cyclobutane, spiro compound

**Experimental procedures:**

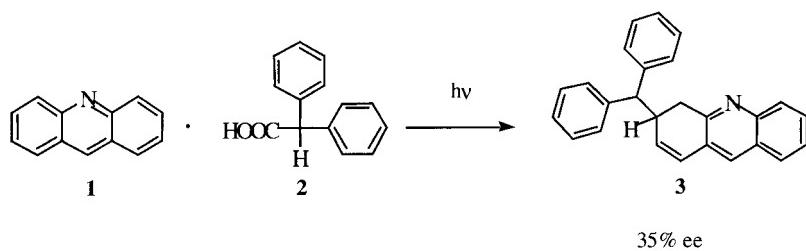
Recrystallization of **1** from MeCN containing **2d** in excess afforded the 1:1 CT crystal as purple plates. The 1:1 CT crystals of **2b** and **2c** were obtained as reddish powders by admixing **1** with **2b** and **2c**, respectively. The 1:1 CT crystal of **1** and **2a** was also isolated as an orange powder by the similar method. Upon irradiation of a fine powder of the 1:1 CT complex with wavelength $\lambda > 505$ nm for 1 h, **3a** was obtained in 71% yield. The adduct **3b** was isolated in 91% yield on irradiation for 1 h with light ($\lambda > 540$ nm).

References: T. Suzuki, T. Fukushima, Y. Yamashita, T. Miyashi, *J. Am. Chem. Soc.*, **116**, 2793 (1994).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: acridine, diphenylacetic acid, photodecarboxylation, two-component molecular crystal, chiral crystal, 7,8-dihydro-7-diphenylmethyl-acridine

**Experimental procedures:**

Chiral two-component crystal (**1·2**, 800 mg) in preparative scale prepared by seeding was pulverized, placed between two Pyrex plates, and irradiated with a

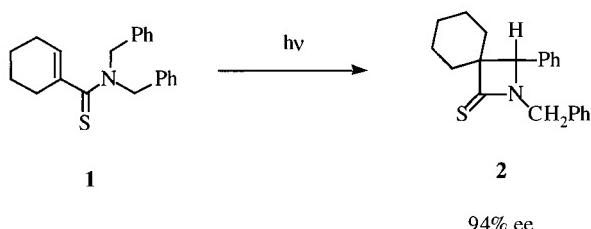
400-W high-pressure Hg lamp for 3 h under argon at room temperature. The irradiated mixture was submitted to preparative TLC (benzene-ethyl acetate, 7:1) to give 260 mg of a chiral condensation product **3** of 35% ee in 37% yield.

References: H. Koshima, K. Ding, Y. Chisaka, T. Matsuura, *J. Am. Chem. Soc.*, **118**, 12059 (1996).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *N,N*-dibenzyl-1-cyclohexenecarbothioamide, chiral crystal, photoirradiation, β -thiolactam, spiro compound



Experimental procedures:

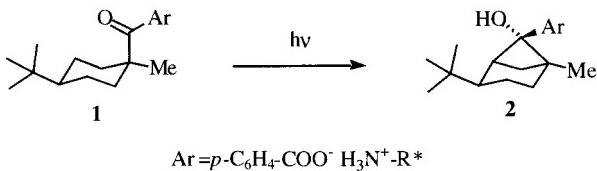
Powdered crystals of **1**, well ground and sandwiched by Pyrex glass plates, were irradiated with 500-W Hg lamp at 0°C for 2 h, which led to the exclusive production of optically active β -thiolactam, 1-benzyl-4-phenyl-azetidine-2-thione-3-spiro-1'-cyclohexane **2**, in 96% yield at 58% conversion. The material was purified by column chromatography, and the structure was determined by spectroscopy. As expected, the thiolactam **2** showed optical activity ($[a]_D^{25} +109^\circ$ c 1.0 CHCl₃, 94% ee).

References: M. Sakamoto, M. Takahashi, K. Kamiya, K. Yamaguchi, T. Fujita, S. Watanabe, *J. Am. Chem. Soc.*, **118**, 10664 (1996).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *cis*-4-*tert*-butylcyclohexyl ketone, Norrish type II photoreaction



H ₃ N-R*	time (min)	ee (%)
(+)-pseudoephedrine	73	79
(+)- α -methylbenzylamine	45	92
(-)-norephedrine	15	96

Experimental procedures:

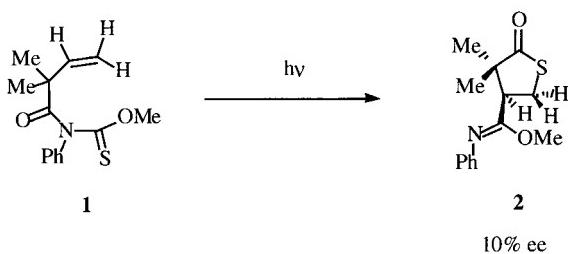
cis-4-*tert*-butylcyclohexyl carboxylic acid **1** was reacted with various optically active amines, and the resulting crystalline salts were then photolyzed in the solid state. The photolysis mixtures were dissolved in a mixture of ethyl acetate and water and treated with excess ethereal diazomethane to form keto ester. This material was freed of the chiral auxiliary by short path silica gel column chromatography and then analyzed by chiral HPLC.

References: M. Leibovitch, G. Olovsson, G. Sundarababu, V. Ramamurthy, J.R. Scheffer, J. Trotter, *J. Am. Chem. Soc.*, **118**, 1219 (1996).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *N*-(2,2-dimethylbut-3-enoyl)-*N*-phenylthiocarbamate, chiral crystal, photoreaction, thiolactone



Experimental procedures:

The solid state photolysis of **1** gave optically active thiolactone **2** ($[a]_{D}^{25} +8^\circ$ (c 1.0, CHCl₃, 10% ee) in 85% yield when the reaction conversion was 78%.

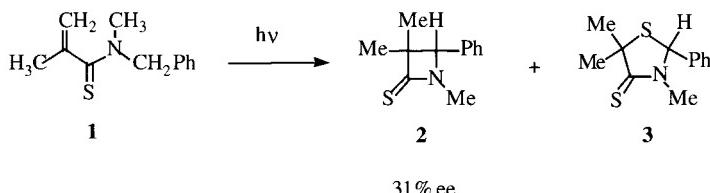
The enantiomeric purity of **2** was determined by HPLC employing a chiral cell OJ (Daicel).

References: M. Sakamoto, M. Takahashi, T. Arai, M. Shimizu, K. Yanaguchi, T. Mino, S. Watanabe, T. Fujita, *Chem. Commun.*, 2315 (1998).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: *N*-benzyl-*N*-methylmethacrylthioamide, photoreaction, β -thiolactam



Experimental procedures:

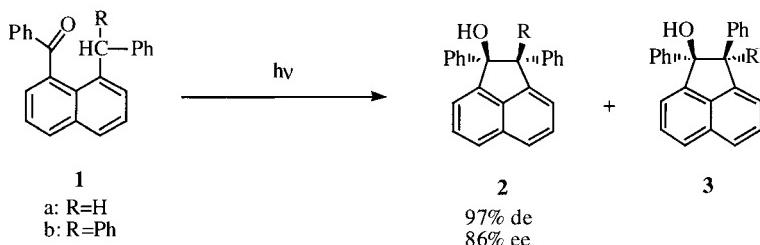
The solid-state photoreaction of thioamide **1** was done under an atmosphere purged with dry argon. The solid sample was irradiated for 4 h as a powder prepared by grinding, and placed inside a Pyrex slide. When powdered thioamide **1** was irradiated in the solid state at 0 °C, at up to 19% conversion, optically active β -thiolactam **2** of 31% ee was isolated. The optical purity was determined by HPLC using a chiral cell OD column (Daicel Chemical Ind.).

References: M. Sakamoto, M. Takahashi, W. Arai, K. Kamiya, T. Mino, S. Watanabe, T. Fujita, *J. Chem. Soc., Perkin Trans. I*, 3633 (1999).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 1-benzoyl-8-benzylnaphthalene, chiral crystal, photoirradiation, topochemistry, *cis*-1,2-diphenylacenaphthen-1-ol

**Experimental procedures:**

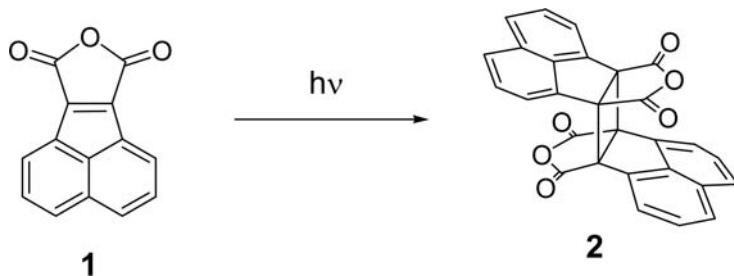
Irradiation of single crystals of **1** in the solid state yields *cis*-1,2-diphenylacet-naphthen-1-ol **2** as main product, with up to 97% de and 86% ee. Only a small amount of *trans*-acenaphthphenol **3** is also generated in the solid state, presumably due to an increased thermal motion of the molecules in the crystal during the irradiation (40–55 °C).

References: H. Irngartiger, P.W. Fettel, V. Siemund, *Eur. J. Org. Chem.*, 3381 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: acenaphthylene-1,2-dicarboxylic anhydride, [2+2]photodimerization

**Experimental procedures:**

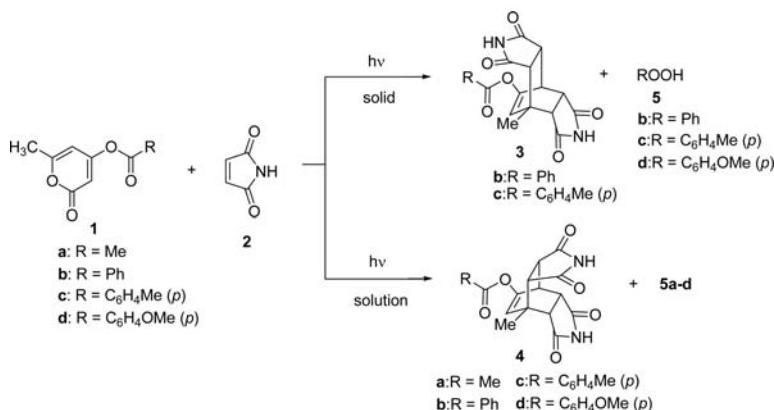
Compound **1** was dissolved in dichloromethane and placed in a photolysis flask. The dichloromethane was evaporated under a stream of nitrogen as the flask was turned slowly. The resulting film was irradiated in air with a 450 W medium pressure mercury lamp with a Pyrex filter for 3 h, producing a nearly quantitative yield of a white dimer **2**.

References: R.D. Rieke, G.O. Page, P.M. Hudnall, R.W. Arhart, T.W. Bouldin, *J. Chem. Soc., Chem. Commun.*, 38 (1990).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: double [4+2]photocycloaddition, 4-acyloxy-2-pyrone, maleimide



Experimental procedures:

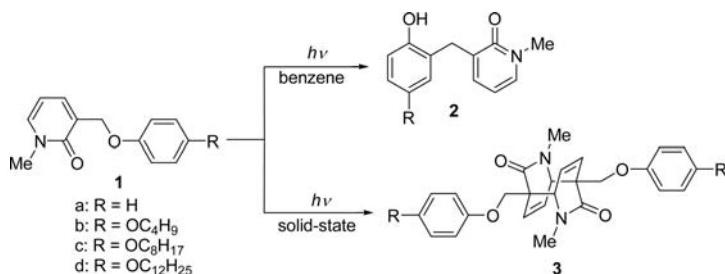
The mixed crystals of **1b** (46 mg, 0.2 mmol), **2** (39 mg, 0.4 mmol), and xanthone (10 mg, 0.05 mmol) prepared by crystallization were ground for 10 min and sandwiched between two Pyrex glass plates and irradiated for 24 h under nitrogen atmosphere at room temperature. The reaction solid was washed with $CHCl_3$ (5 mL) to remove the starting materials and the resulting solid was filtered to give **3b** (40 mg, 52% yield), which was recrystallized from MeCN.

References: T. Shimo, M. Matsushita, H. I. Omar, K. Somekawa, *Tetrahedron*, **61**, 8059 (2005).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: [4+4]photodimerization, 2-pyridone



Experimental procedures:

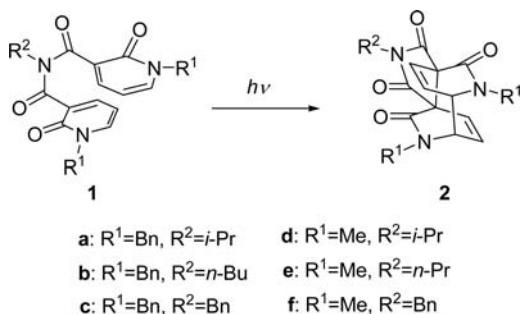
Powdered crystals of **1a** (50 mg, 0.29 mmol) sandwiched between two cover glasses and placed in a polyethylene bag, were irradiated externally for 20 h with a 400 W high-pressure mercury lamp in an ice–water bath (ca. 0 °C) through a Pyrex filter. Conversion of **1a** to the photodimer **3a** was quantitative, which was confirmed from the ¹H NMR spectrum of the irradiated crystals. They showed the exact spectrum corresponding to **3a** without purification and even traces of **1a** and the rearrangement product **2a** could not be detected. In a similar manner, **3c** and **3d** were prepared in quantitative yield with complete conversion from **1c** and **1d**, respectively.

References: S. Kohmoto, T. Noguchi, H. Masu, K. Kishikawa, M. Yamamoto, K. Yamaguchi, *Org. Lett.*, **6**, 683 (2004).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: [4+4]photodimerization, 2-pyridone derivative

**Experimental procedures:**

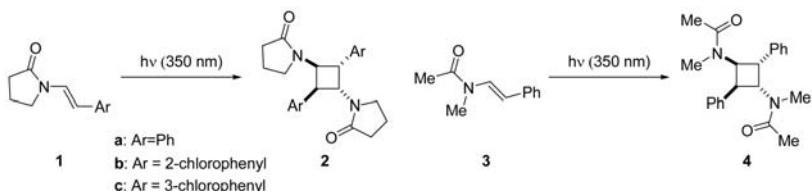
Ground crystals of **1a** (0.020 g, 0.042 mmol) were placed between two glass plates. The sandwiched sample was placed in a transparent polyethylene bag. UV irradiation was carried out externally on this sample with a 400 W high-pressure mercury lamp through a Pyrex filter for 6 h at ca. 23 °C in a water bath. Without purification, **2a** was obtained as a pure product in quantitative yield. The photocycloadduct **2a** was recrystallized from hexane/ethyl acetate to give colorless crystals. Similarly other [4+4]photocycloadducts **2b–2h** were obtained.

References: H. Masu, K. Ohmori, K. Kishikawa, M. Yamamoto, K. Yamaguchi, S. Kohmoto, *Bull. Chem. Soc. Jpn.*, **78**, 1127 (2005).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: cyclobutane, [2+2]photodimerization, enamide



Experimental procedure:

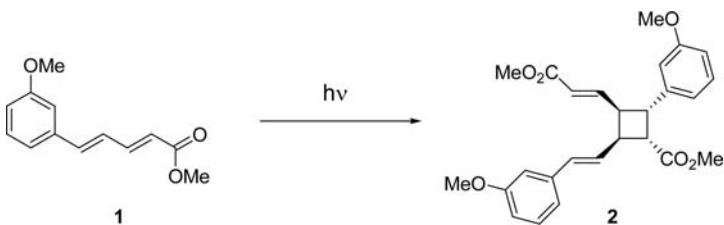
Irradiation of 58 mg of **1a** in a pyrex dish at 350 nm for 23 h resulted in quantitative conversion to **2a**, as determined by analysis of the ¹H NMR spectrum. Purification by flash chromatography on silica gel (1:1 EtOAc/CHCl₃) gave 51 mg (87%) of pure **2a**: mp 196.5–198 °C. Irradiation of 67 mg of **3** in a pyrex dish at 350 nm for 21 h resulted in quantitative conversion to **4**, as determined by analysis of the ¹H NMR spectrum. Purification by flash chromatography on silica gel (1:1 EtOAc/CHCl₃) gave 60 mg (89%) of pure **4**: mp 177–179 °C.

References: F. Song, J.H. Snook, B.M. Foxman, B.B. Snider, *Tetrahedron*, **54**, 13035 (1998).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: [2+2]photodimerization



Experimental procedures:

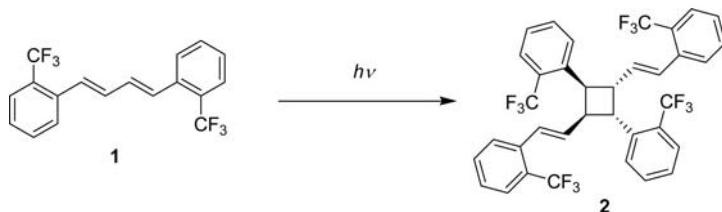
When a sample of **1** (mp 62–64 °C, recrystallized from Et₂O–hexane) was placed between two layers of Pyrex glass and irradiated with ultraviolet light from a Hanovia medium-pressure Hg lamp, the reaction proceeded cleanly to produce the monocyclobutane head-to tail derivative **2** in 63% isolated yield (80% conversion after 7 h).

References: V. Mascitti, E.J. Corey, *Tetrahedron Lett.*, **47**, 5879 (2006).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: [2+2]photodimerization, *E,E*-1,4-di(*o*-trifluoromethyl)phenyl-1,3-butadiene



Experimental procedures:

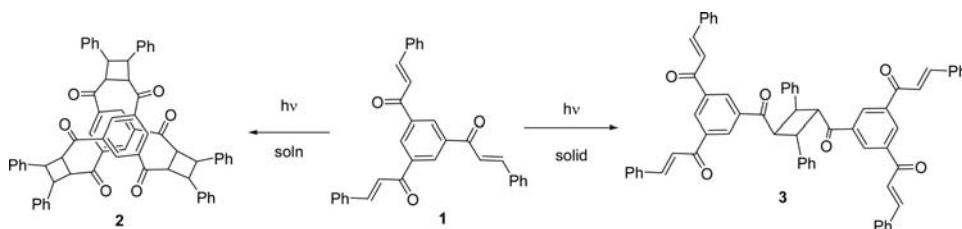
UV-irradiation of **1** in solution using a 200 W Hg medium-pressure lamp with a Pyrex filter resulted in the conversion of **1** to its *Z,E* isomer in >95% yield. On the other hand, UV photolysis of the powdered crystalline sample **1** using the same light source at room temperature for 15 h afforded a single product **2** in 100% yield.

References: J. Liu, K.J. Boarman, *Chem. Comm.*, 340 (2005).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: [2+2]photodimerization, 1,3,5-tris(3-phenylpropenoyl)benzene



Experimental procedures:

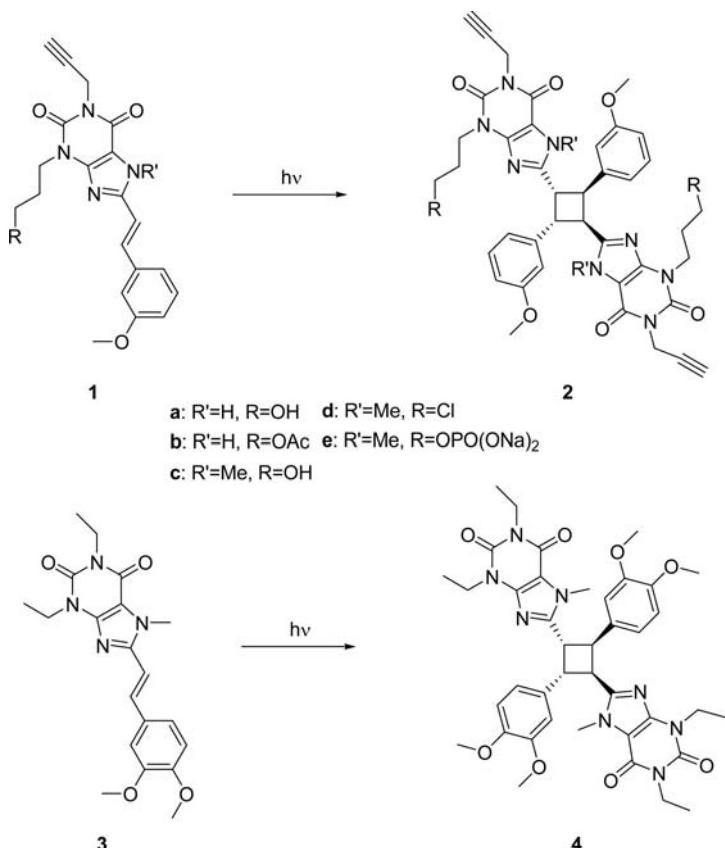
Irradiation (>290 nm) of **1** in the crystalline state afforded a dimer **3** (80%), which contains only one four-membered ring and has the head-to-tail/*anti* structure.

References: H. Meier, E. Karpouk, *Tetrahedron Lett.*, **45**, 4477 (2004).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: [2+2]photodimerization, A_{2A} adenosine receptor antagonists



Experimental procedures:

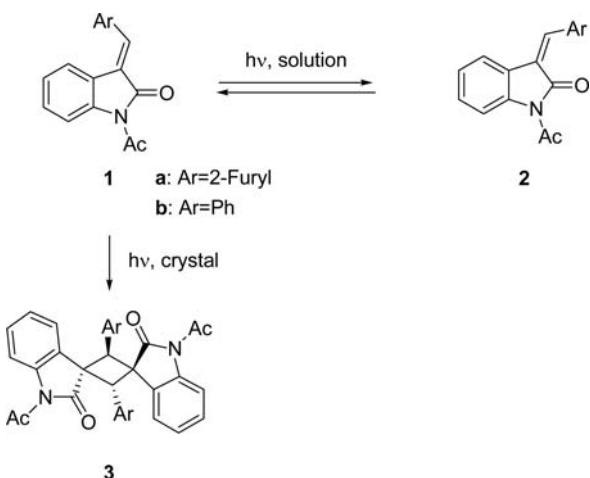
A crystal film of 100 mg (0.25 mmol) of **1c** was prepared by dissolving the yellowish solid in a minimum of CH_2Cl_2 and subsequently leaving the solvent to evaporate on the surface of a photoreactor. After 90 min of irradiation, the essentially decolorized product was dissolved in CH_2Cl_2 , filtered to remove oligomeric material, and recrystallized by the addition of diethyl ether to yield colorless crystals of **2c** (63 mg): mp 252 °C dec.

References: J. Hockemeyer, J.C. Burbiel, C.E. Müller, *J. Org. Chem.*, **69**, 3308 (2004).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: [2+2]photodimerization, 2-furylidenoindole, benzylidenoindole



Experimental procedures:

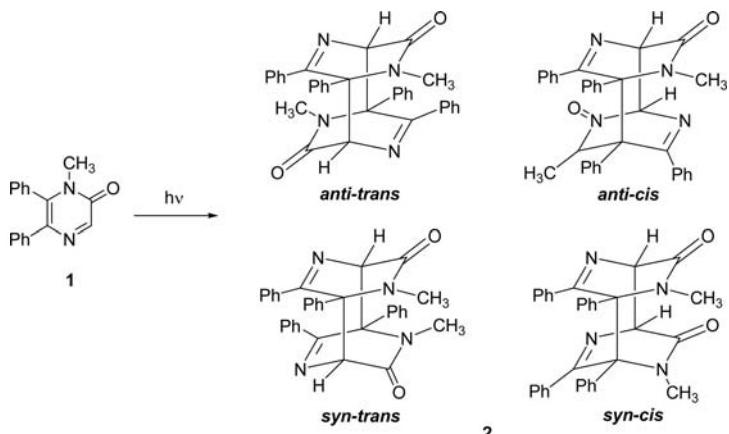
A finely ground sample of compound **1a** (200 mg) was evenly spread on a 5 cm × 20 cm glass plate and exposed to the light from two 15 W phosphor-coated lamps (366 nm) at 10 cm distance. The powder was occasionally mixed. After 10 h, the powder was washed with a little chloroform, dissolving some unreacted starting material. The colorless residue (140 mg) was practically pure dimer **3a**, as shown by the spectrum. This could be recrystallized from nitro-methane.

References: M. Milanesio, D. Viterbo, A. Albini, E. Fasani, R. Bianchi, M. Barzaghi, *J. Org. Chem.*, **65**, 3416 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: [4+4]photodimerization, 1-methyl-5,6-diphenylpyrazin-2-one

**Experimental procedures:**

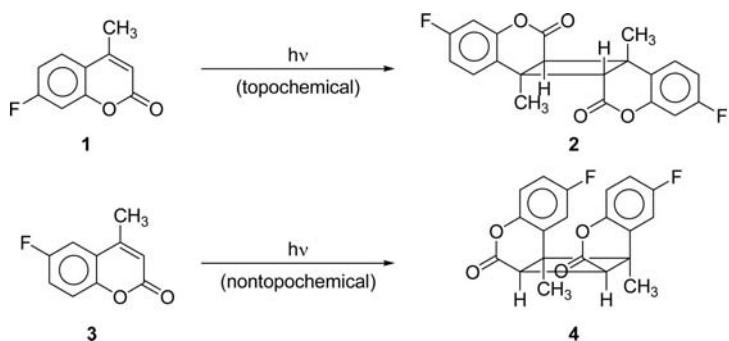
A single crystal of **1** (23 mg, 0.09 mmol) was photolyzed for 20 h with a medium-pressure mercury lamp equipped with a Pyrex filter. The resulting solid was dissolved in a small amount of ethyl acetate, and the photodimer **2** was isolated by column chromatography with 20% diethyl ether in petroleum ether (v/v). Recrystallization from ethyl acetate gave colorless needles (17 mg, 74%, mp 148–150 °C).

References: M. Kaftory, V. Shtelman, T. Lavy, J. R. Scheffer, J. Yang, V. Enkelmann, *Eur. J. Org. Chem.*, 847 (2005).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 6-fluoro-4-methylcoumarin, 7-fluoro-4-methylcoumarin, [2+2]photodimerization



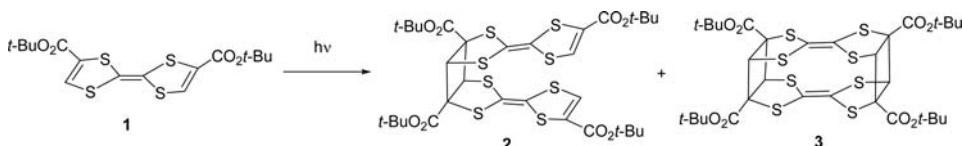
Experimental procedures:

Finely powdered crystalline samples of **1** and **2**, placed at a distance of ca. 30 cm from the Rayonet photochemical lamps (max = 320 nm \pm 20) were irradiated simultaneously for about 35–45 h. During irradiation, care was taken to expose the samples uniformly by shaking the containers at regular intervals. Uniform temperature in the irradiation chamber was ensured by keeping a cooling fan on during irradiation. The photoproducts were separated from their monomers by column chromatography on silica gel using 10% ethyl acetate in petroleum ether as eluent. The percentage conversion was 20–25% for **1** and 25–30% for **2**, as determined from ^1H NMR.

References: K. Vishnumurthy, T. N. Guru Row, K. Venkatesan, *Tetrahedron*, **54**, 11235 (1998).

Type of reaction: C–C bond formation**Reaction condition:** solid-state

Keywords: [2+2]photodimerization, tetrathiafulvalene

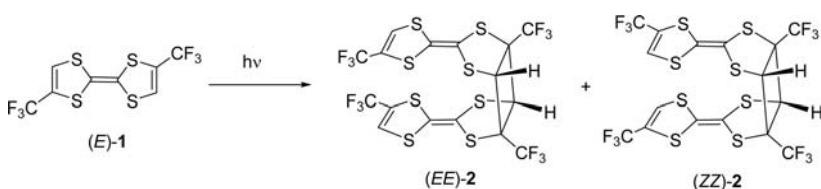
**Experimental procedures:**

Finely powdered CISTF **1** (80 mg, 20 mmol) was put in a sealed glass tube and kept in sunlight for 2 days. The sample was shaken from time to time. During irradiation, the deep orange color of the compound changed to yellow. Chromatography on a column of silica gel (particle size 0.2–0.5 mm, length 20 cm, diameter 1 cm) packed with hexane and elution with chloroform-hexane (70:30) gave the first fraction as the cage product **3** (52 mg, 65%) and the second fraction as **2** (24 mg, 39%).

References: P. Venugopalan, K. Venkatesan, *Bull. Chem. Soc. Jpn.*, **63**, 2368 (1990).

Type of reaction: C–C bond formation**Reaction condition:** solid-state

Keywords: [2+2]photodimerization, tetrathiafulvalene



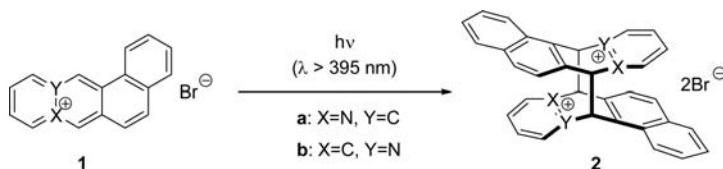
Experimental procedures:

Orange crystals of compound (*E*)-**1** that were allowed to stand in the sunlight for 2 weeks at room temperature slowly lost their crystallinity and turned yellow. The starting TTF derivative (*E*)-**1** was eliminated by washing with pentane. Recrystallization from EtOH afforded derivative (*EE*)-**2** as elongated thin plates together with microcrystalline yellow powder. ^{19}F and ^1H NMR measurements on this mixture revealed the presence of about 20% of product (*ZZ*)-**2**.

References: O. Jeannin, M. Fourmigue, *Chem. Eur. J.*, **12**, 2994 (2006).

Type of reaction: C–C bond formation**Reaction condition:** solid-state

Keywords: [4+4]photodimerization, naphthoquinolizinium salts

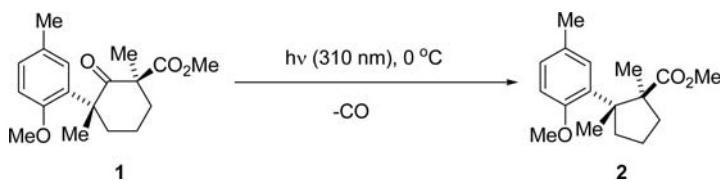
**Experimental procedures:**

Naphtho[1,2-*b*]quinolizinium bromide (**1a**) was crystallized from ethanol. The ground crystals (14.3 mg, 43.6 mol) were irradiated under argon for 60 h at 10 °C. The resulting pale yellow solid was crystallized from methanol to give the dimer *anti-ht*-**2a** (7.4 mg, 11.2 mol, 51%) as pale yellow cubes; mp 304–306 °C [dec. at 240–250 °C, thermal cycloreversion was indicated by a color change from pale yellow to green; mp (**1a**): 302–303 °C].

References: H. Ihmels, D. Leusser, M. Pfeiffer, D. Stalke, *J. Org. Chem.*, **64**, 5715 (1999); H. Ihmels, C.J. Mohrschladt, A. Schmitt, M. Bressanini, D. Leusser, D. Stalke, *Eur. J. Org. Chem.*, 2624 (2002).

Type of reaction: C–C bond formation**Reaction condition:** solid-state

Keywords: herbertenolide, photodecarbonylation



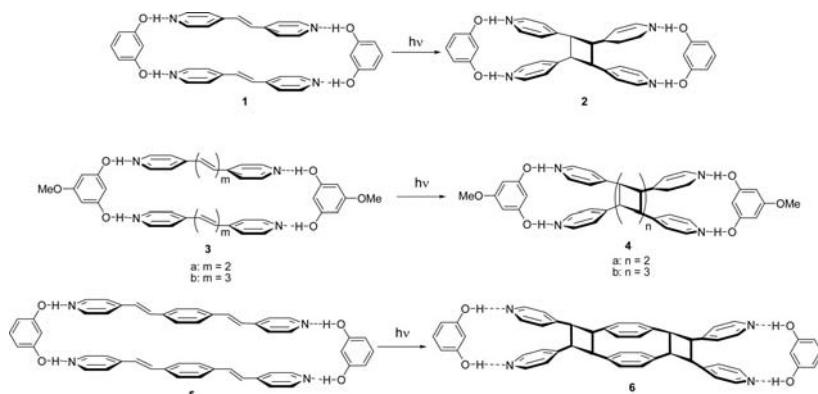
Experimental procedures:

The photolysis of finely powdered samples of crystalline **1** with a medium Hanovia mercury lamp at 0 °C for 6–12 h occurred with remarkably high chemo- and stereoselectivity. ¹H NMR and GC-MS analysis revealed the formation of the desired cyclopentanone **2** in ca. 76% yield with no trace of the cis-diastereoisomer after 20% conversion.

References: D. Ng, Z. Yang, M. A. Garcia-Garibay, *Org. Lett.*, **6**, 645 (2004); M. J. E. Resendiz, M. A. Garcia-Garibay, *Org. Lett.*, **7**, 371 (2006).

Type of reaction: C–C bond formation**Reaction condition:** solid-state

Keywords: [2+2]photodimerization, resorcinol, 1,2-bis(4-pyridyl)ethylene

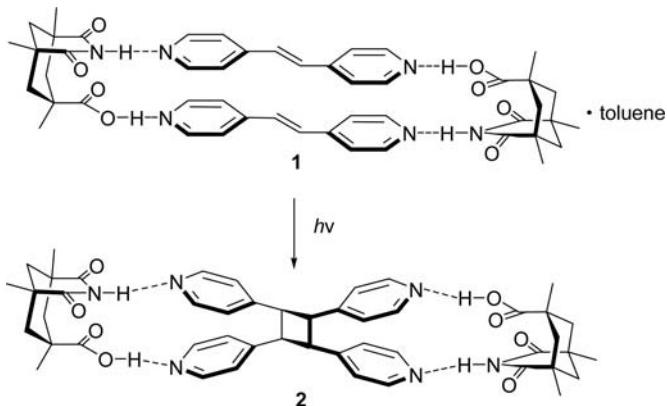
**Experimental procedures:**

UV irradiation of a powdered crystalline sample of **1** placed between two glass plates (Hg lamp) produced *rctt*-tetrakis(4-pyridyl)cyclobutane (**2**), stereospecificity (yield: 100%), after a period of 42 h.

References: L. R. MacGillivray, J. L. Reid, J. A. Ripmeester, *J. Am. Chem. Soc.*, **122**, 7817 (2000); T. D. Hamilton, G. S. Papaefstathiou, L. R. Macgillivray, *CrystEngComm.*, **4**, 223 (2002); T. Friscic, L. R. MacGillivray, *Chem. Commun.*, 1306 (2003); T. Friscic, D. M. Drab, L. R. MacGillivray, *Org. Lett.*, **6**, 4647 (2004); X. Gao, T. Friscic, L. R. MacGillivray, *Angew. Chem. Int. Ed.*, **43**, 232 (2004).

Type of reaction: C–C bond formation**Reaction condition:** solid-state

Keywords: [2+2]photodimerization, 1,2-bis(4-pyridyl)ethylene, cyclobutane

**Experimental procedures:**

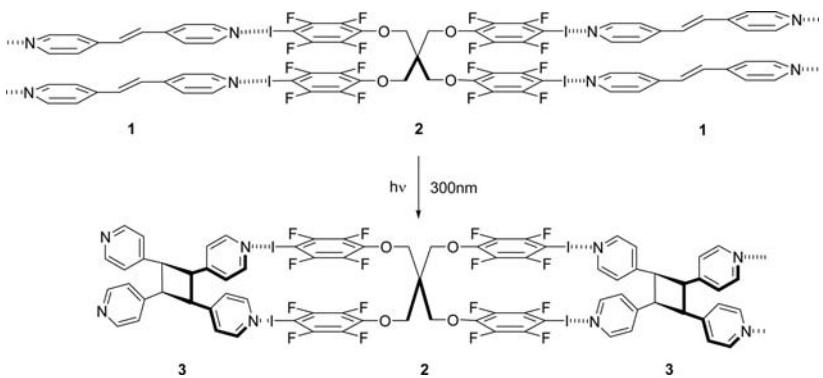
The UV-irradiation experiments were performed by placing either single crystals or finely ground samples of **1**·toluene between pyrex plates and turning the sample to ensure uniform irradiation.

References: D.B. Varshney, X. Gao, T. Friščić, L.R. MacGillivray, *Angew. Chem. Int. Ed.*, **45**, 646 (2006).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 1,2-bis(4-pyridyl)ethylene, halogen-bonding, [2+2]photodimerization

**Experimental procedures:**

Co-crystal **1–2** (62.6 mol, 100 mg) was finely powdered and spread as a thin layer between two quartz-glass plates, then it was irradiated for 3 h at $\lambda=300$ nm under TLC control (EtOAc/MeOH, 7:3). The resulting yellow solid

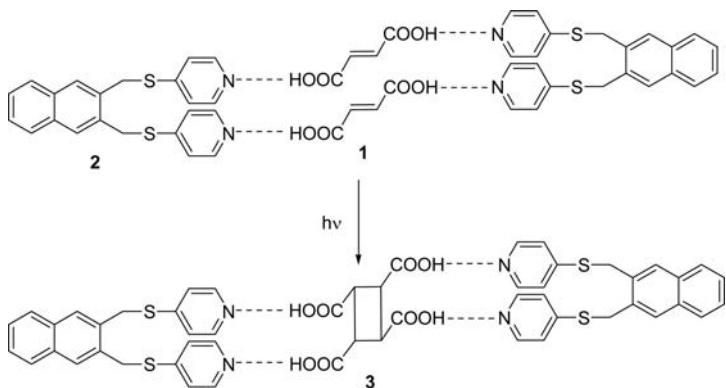
(100 mg, 100%) was analyzed by NMR and FT-IR. Isolation of *r*-1,2,3,4-tetra-(4-pyridyl)cyclobutane **3** was achieved by flash-chromatography, mp 507 K.

References: T. Caronna, R. Liantonio, T.A. Logothetis, P. Metrangolo, T. Pilati, G. Resnati, *J. Am. Chem. Soc.*, **126**, 4500 (2004).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: [2+2]photodimerization, 2,3-bis(4-methylenethiopyridyl)naphthalene



Experimental procedures:

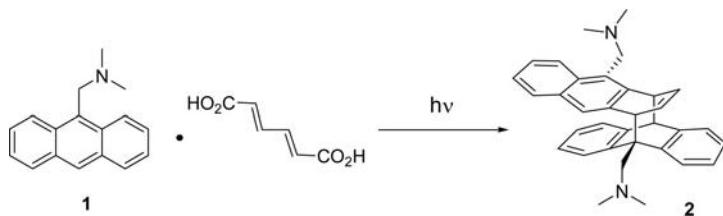
Ultraviolet irradiation of a powdered crystalline sample of 2(2,3- bis(4-methylenethiopyridyl)naphthalene, **2**)-2(fumaric acid, **1**) using 300 nm light (Rayonet reactor) for 10 days produced *rctt*-1,2,3,4-tetracarboxylic acid **3** in 70% yield.

References: T. Friscic, L.R. MacGillivray, *Chem. Commun.*, 5748 (2005).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: [4+4]photodimerization, 9-aminomethylanthracene



Experimental procedures:

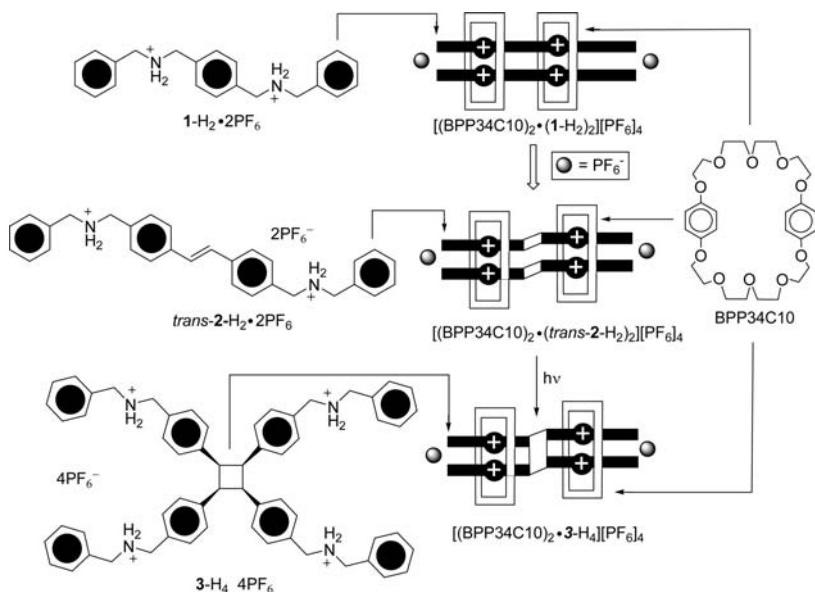
Irradiation was carried out with a 400 W high-pressure mercury lamp. A powdered solid sample was sandwiched between two Pyrex plates and placed in a polyethylene bag. The irradiation was carried out under an Ar atmosphere. During the irradiation, the samples were cooled by refrigerated circulating water (3–7 °C). After irradiation of the crystalline salt **1**, the reaction mixture was neutralized with an aqueous solution of K_2CO_3 and extracted with CH_2Cl_2 . Preparative thin-layer chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) gave a mixture of **2** and **1**. Crystallization from MeOH gave pure **2**.

References: M. Horiguchi, Y. Ito, *J. Org. Chem.*, **71**, 3608 (2006).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: [2+2]photodimerization, bis-*p*-phenylene[34]crown-10



Experimental procedures:

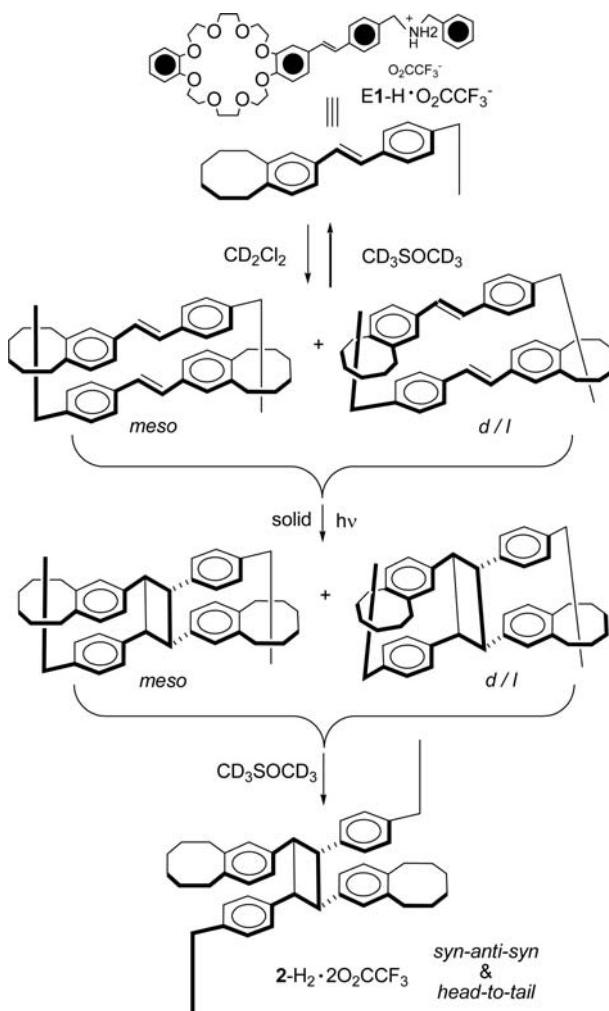
Crystals (421 mg, 0.169 mmol) of $[(\text{BPP}_{34}\text{C}_{10})_2\text{-}(\text{trans-2-H}_2)_2]\text{[PF}_6\text{]}_4$ were powdered and then irradiated for 30 h with UV light from a Hanovia lamp in a rotating Pyrex tube attached to a Kugelrohr apparatus.

References: D.G. Amirsakis, M.A. Garcia-Garibay, S.J. Rowan, J.F. Stoddart, A.J.P. White, D.J. Williams, *Angew. Chem. Int. Ed.*, **40**, 4256 (2001).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: [2+2]photodimerization, bis([18]crown-6)-substituted stilbene



Experimental procedures:

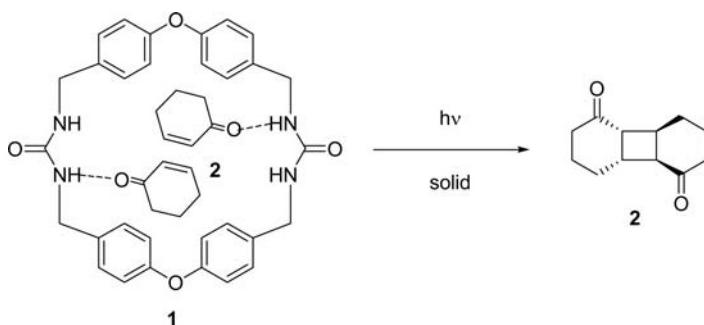
Crystals were grown by layering hexanes over a solution of *E*-1-H-O₂CCF₃ (5 mg) in CH₂Cl₂ (0.5 mL). The crystals were filtered, air-dried, placed between two pyrex microscope slides and then irradiated for about 3 h to give 2-2H₂-O₂CCF₃ (5 mg, 100%) as a white solid.

References: D.G. Amirsakis, A.M. Elizarov, M.A. Garcia-Garibay, P.T. Glink, J.F. Stoddart, A.J.P. White, D.J. Williams, *Angew. Chem. Int. Ed.*, **42**, 1126 (2003).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: bisurea, 2-cyclohexenone, [2+2]photodimerization

**Experimental procedures:**

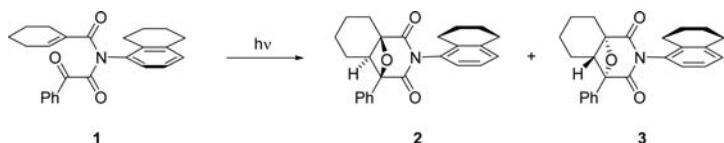
The apohost **1**-2-cyclohexenone complex was irradiated under UV light at room temperature with a Hanovia 450 W medium-pressure mercury lamp. After 24 h, dimer **2** was the major product and no enone was detectable by ¹H NMR or GC/MS. The photoproducts could be separated from apohost **1** by washing with CH₂Cl₂, and apohost **1** was recovered.

References: J. Yang, M.B. Dewal, L.S. Shimizu, *J. Am. Chem. Soc.*, **128**, 8122 (2006).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: asymmetric synthesis, chiral crystal, oxetane

**Experimental procedures:**

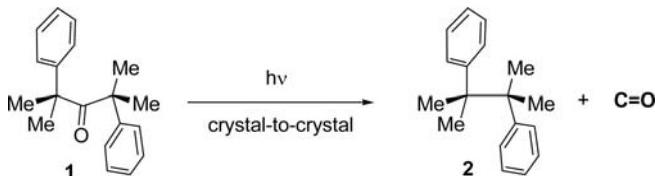
The solid-state photoreaction was carried out under an atmosphere of dried argon. When the solid samples were irradiated as powders in a Pyrex tube for 1 h, bicyclic oxetanes (**2**, **3**) were obtained quantitatively in a **2**:**3** ratio of 95:5. The major isomer **2** could be isolated by column chromatography on silica gel, and the optical purity was determined by HPLC by using a chiralcel OJ column as >99% ee, whereas the minor isomer **3** could not be isolated in the pure form.

References: M. Sakamoto, T. Iwamoto, N. Nono, M. Ando, W. Arai, T. Mino, T. Fujita, *J. Org. Chem.*, **68**, 942 (2003).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: dicumyl ketone, photodecarbonylation, crystal-to-crystal reaction

**Experimental procedures:**

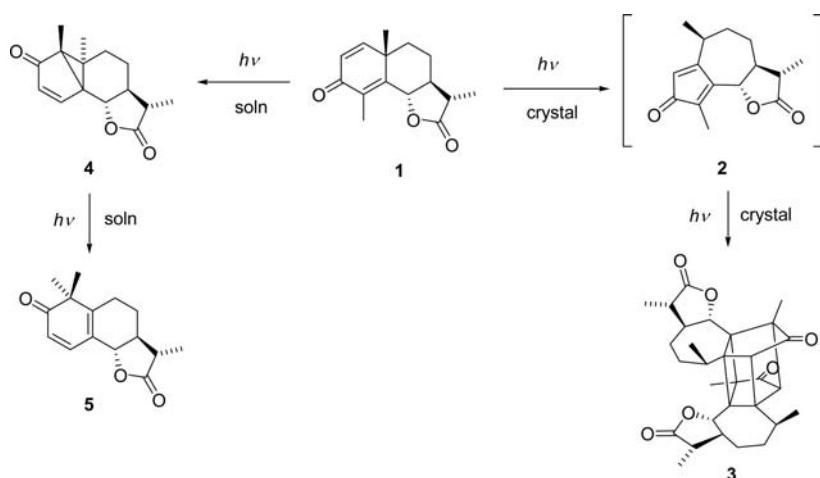
Crystals grown from ethanol by slow evaporation were ground with a mortar and pestle to an approximate size of 15–55 m, as judged by optical microscopy. To disperse the crystals in water the surface tension had to be reduced to prevent agglomeration; this was accomplished by adding SDS. The crystals tended to settle downward slowly and after 5–6 h almost all the crystals were on the bottom. To expose all crystals equally to the light, the suspension was magnetically stirred.

References: M. Veerman, M.J.E. Resendiz, M.A. Garcia-Garibay, *Org. Lett.*, **8**, 2615 (2006).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: Diels-Alder reaction, [2+2]photodimerization, α -santonin



Experimental procedures:

Santonin crystals (250 mg) were crushed between two Pyrex plates and photolyzed with a Hanovia 400 W lamp for 3 days. The bright yellow powder was dissolved in 50 mL of ethyl acetate. The reaction mixture was analyzed using GC, IR and NMR. The solvent was removed and the residue was chromatographed over silica (ether:hexane = 30:70).

References: A. Natarajan, C. K. Tsai, S. I. Khan, P. McCarren, K. N. Houk, M. A. Garcia-Garibay, *J. Am. Chem. Soc.*, **129**, 9846 (2007).

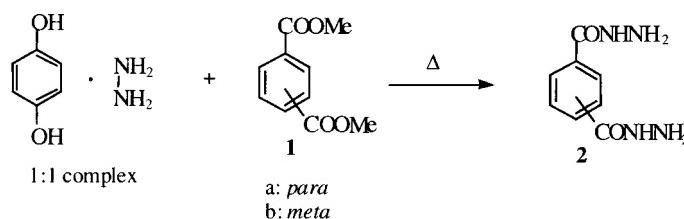
4 Carbon–Nitrogen Bond Formation

4.1 Solvent-Free C–N Bond Formation

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: anhydrous hydrazine, hydroquinone, dimethyl terephthalate, inclusion crystal, terephthalic acid dihydrazide



Experimental procedures:

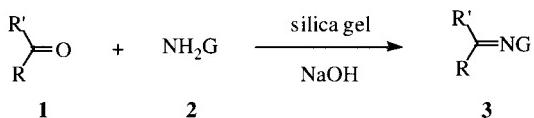
A mixture of powdered dimethyl terephthalate **1a** (19.4 g, 0.1 mol) and 1:1 inclusion complex of hydroquinone and hydrazine (58.5 g, 0.4 mol) was kept under a nitrogen atmosphere at 100–125 °C for 25 h. To the reaction mixture was added MeOH and MeOH insoluble terephthalic acid dihydrazide **2a** was obtained by filtration (17.1 g, 88.1% yield).

References: F. Toda, S. Hyoda, K. Okada, K. Hirotsu, *Chem. Commun.*, 1531 (1995).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: aldehyde, ketone, hydrazin derivative, semicarbazide, NaOH, silica gel, hydrazone, semicarbazide



- a: R=R'=Ph, G=PhNH
- b: R=Me, R'=Ph, G=PhNH
- c: R=Me, R'=3,4-(MeO)₂C₆H₃, G=PhNH
- d: R=Me, R'=4-PhC₆H₄, G=PhNH
- e: R=Ph, R'=2-pyridyl, G=PhNH
- f: R=Me, R'=2-pyridyl, G=PhNH
- g: R=Me, R'=4-MeOC₆H₄, G=PhNH
- h: R=Me, R'=2-MeOC₆H₄, G=PhNH
- i: R=R'=Ph, G=4-NO₂C₆H₄NH
- j: R=H, R'=4-MeOC₆H₄, G=4-NO₂C₆H₄NH
- k: R=Me, R'=4-ClC₆H₄, G=4-NO₂C₆H₄NH
- l: R=Me, R'=4-PhC₆H₄, G=4-NO₂C₆H₄NH
- m: R=R'=Ph, G=NMe₂
- n: R=Me, R'=Ph, G=NMe₂
- o: R=Me, R'=3,4-(MeO)₂C₆H₃, G=NMe₂
- p: R=Me, R'=4-MeOC₆H₄, G=NMe₂
- q: R=H, R'=Ph, G=NH₂CONH
- r: R=Me, R'=Ph, G=NH₂CONH
- s: R=Me, R'=4-MeOC₆H₄, G=NH₂CONH
- t: R=Me, R'=3,4-(MeO)₂C₆H₃, G=NH₂CONH

Experimental procedures:

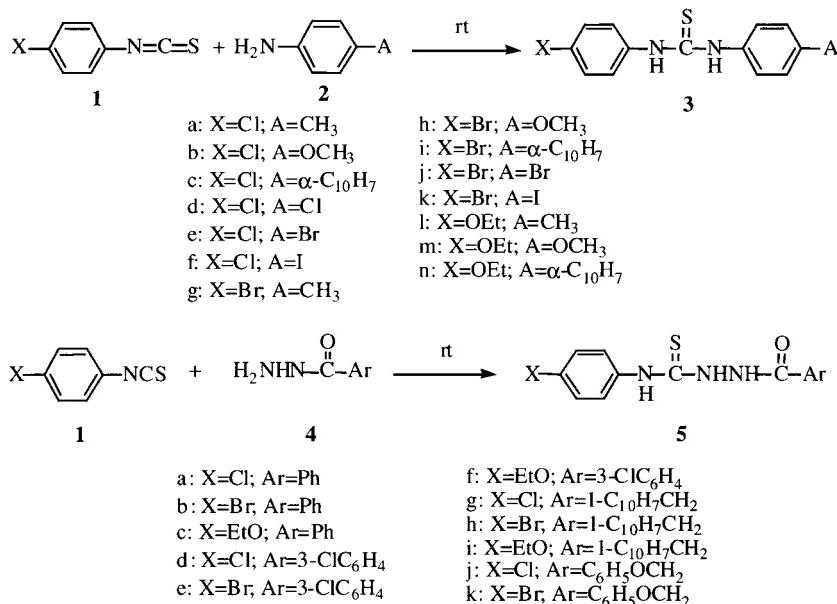
A mortar was charged with the aldehyde or ketone (1 mmol), hydrazine derivative or semicarbazide (1 mmol), sodium hydroxide (0.04 g, 1 mmol) and silica gel (0.1 g). The reaction mixture was ground with a pestle in the mortar. When TLC showed no remaining aldehyde or ketone, the reaction mixture was poured into a mixture of dichloromethane (20 mL) and 5% HCl (10 mL). The ethereal layer was washed with saturated NaHCO₃, dried (MgSO₄), and evaporated by rotary evaporation to give the pure product.

References: A. R. Hajipour, I. Mohammadpoor-Baltork, M. Bigdeli, *J. Chem. Res. (S)*, 570 (1999).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: aryl isothiocyanate, aromatic primary amine, diaryl thiourea



Experimental procedures:

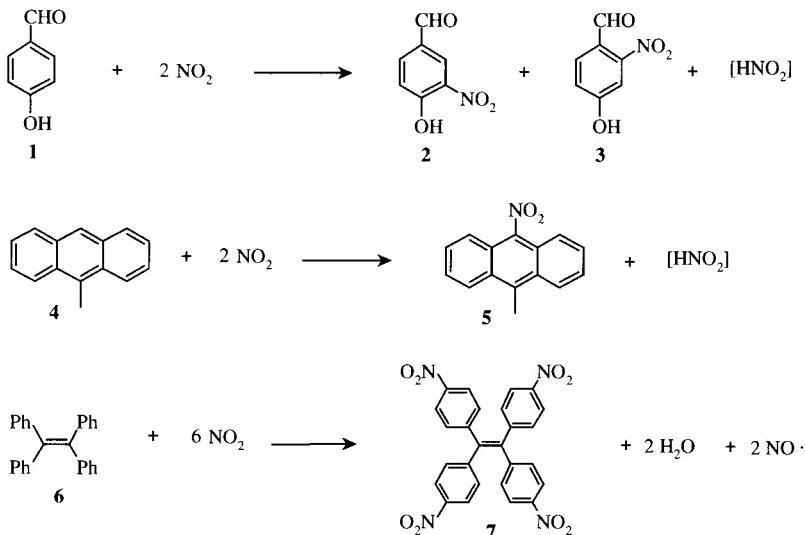
A mixture of aryl isothiocyanate **1** (1 mmol) and aromatic primary amine **2** (1 mmol) was ground thoroughly in an agate mortar. The reaction was traced with thin-layer chromatography. After the reaction was complete (5–40 min), the crude products were recrystallized with ethanol or acetone and dried under vacuum to yield the pure products.

References: J.-P. Li, Y.-L. Wang, H. Wang, Q.-F. Luo, X.-Y. Wang, *Synth. Commun.*, **31**, 781 (2001); J.-P. Li, Q.-F. Luo, Y.-L. Wang, H. Wang, *Synth. Commun.*, **31**, 1793 (2001).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: arenes, nitrogen dioxide, nitration, gas-solid reaction



Experimental procedures:

2/3: 4-Hydroxybenzaldehyde **1** (500 mg, 4.1 mmol) was reacted with NO2 at an initial pressure of 0.3 bar for 12 h. After evaporation of the gases, the product mixture (685 mg, 100%) contained 82% **2** and 18% **3** according to ¹H NMR analysis. The mixture was separated by preparative layer chromatography (SiO2, EtOAc) to isolate 528 mg (77%) of **2**, mp 143 °C and 116 mg (17%) of **3**, mp 104 °C.

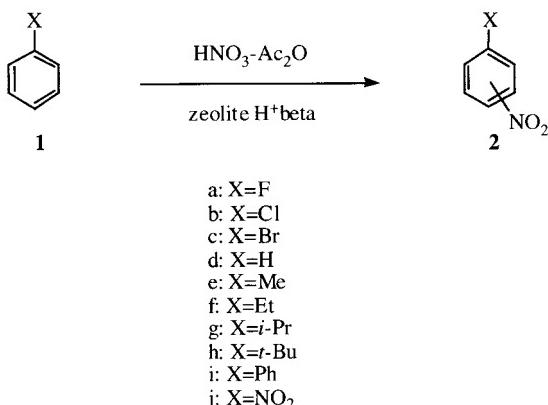
7: Tetraphenylethene **6** (800 mg, 2.41 mmol) was mixed with 800 mg of MgSO4 · 2H2O (for the absorbance of the water of reaction). After 12 h of reaction with NO2 (710 mg, 15.4 mmol) at an initial pressure of 0.3 bar at room temperature, the excess gas and NO were condensed in a cold trap at -196 °C and analyzed by FT-IR (NO/NO2 = 10/2). The quantitatively formed product **7** was extracted from the drying agent with CH2Cl2, yielding pure **7** (1.17 g, 95%), mp 300–302 °C. For larger runs the use of a flow apparatus is advisable, which allows for circulating of the gas and admixing of the calculated amount of oxygen to oxidize the NO formed for use in the running reaction.

References: G. Kaupp, J. Schmeyers, *J. Org. Chem.*, **60**, 5494 (1995).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: aromatic compound nitric acid, acetic anhydride, zeolite, nitration, aromatic nitro compound

**Experimental procedures:**

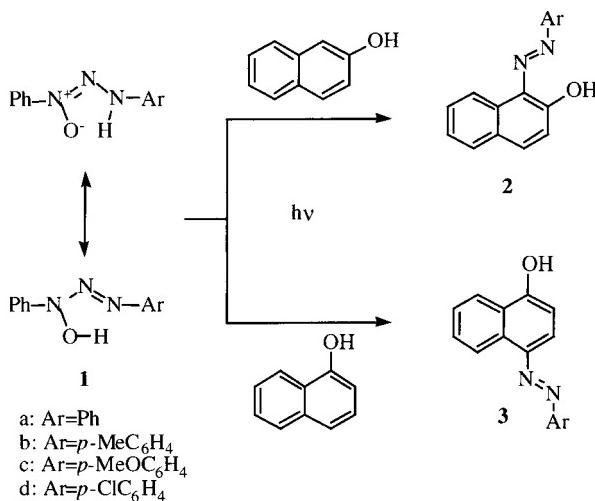
Nitric acid (2.45 g, 90%, 35 mmol) and dried H⁺beta (1.0 g) were stirred together at 0 °C for 5 min. Addition of acetic anhydride (5 mL, 53 mmol) resulted in an exothermic reaction causing a temporary rise in temperature to ca. 10–15 °C. After a further 5 min the aromatic substrate (35 mmol) was added dropwise and the mixture was then allowed to warm to room temperature and stirred for a further 30 min. The products were obtained by direct vacuum distillation of the mixture, first at 30 mmHg to give the acetic acid by product and then at 0.2 mmHg, to give the nitro compound.

References: K. Smith, A. Musson, G. A. DeBoos, *Chem. Commun.*, 469 (1996).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: triazene-1-oxide, naphthol, mixed crystals, photoreaction, azo dye

**Experimental procedures:**

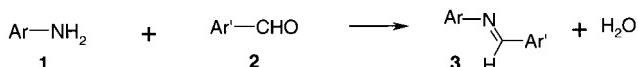
Mixing of 1 mmol of triazene 1-oxide **1** with 1 mmol of *α*- or *β*-naphthol in acetone followed by evaporation gave the mixed crystals. These were finely ground in a mortar, spread on petri dishes and directly exposed to sunlight. TLC examination showed that the reactions were finished within 7–10 h. The temperature was measured as 18 to 25 °C. Chromatographic separation on silica gel with ethyl acetate-toluene (1:10) as eluent gave two zones. The first zone with the higher *R_f* value (at the start) afforded a multicomponent mixture, which could neither be separated nor could individual components be identified.

References: S. K. Mohamed, A. M. N. El-Din, *J. Chem. Res. (S)*, 508 (1999).

Type of reaction: C–N bond formation

Reaction conditions: solvent-free, solid-state

Keywords: anilines, benzaldehydes, condensation, waste-free, azomethines



- | | |
|---|--|
| a: Ar=4-MeC ₆ H ₄ | a: Ar'=4-MeC ₆ H ₄ |
| b: Ar=4-MeOC ₆ H ₄ | b: Ar'=4-MeOC ₆ H ₄ |
| c: Ar=4-NO ₂ C ₆ H ₄ | c: Ar'=4-NO ₂ C ₆ H ₄ |
| d: Ar=4-ClC ₆ H ₄ | d: Ar'=4-HOC ₆ H ₄ |
| e: Ar=4-BrC ₆ H ₄ | e: Ar'=4-HO, 3-MeOC ₆ H ₃ |
| f: Ar=4-HOC ₆ H ₄ | |
| g: Ar=4-(4-H ₂ N ₂ C ₆ H ₄)C ₆ H ₄ | |
| h: Ar=1-naphthyl | |

Experimental procedures:

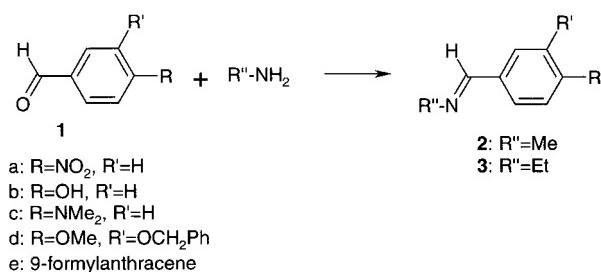
All reactions were performed by grinding together 10 mmol of the pure aniline **1** with 10 mmol of the pure aldehyde **2** in a mortar and keeping the mixture at room temperature. Some mixtures liquefied intermediately at room temperature, but most of these could be run without melting at lower temperatures. The completion of the reactions was checked by IR spectroscopy in KBr. The water produced in the reaction was removed at 80 °C under vacuum. The yield was 100% at 100% conversion in the twenty studied combinations of **1** and **2**. Chemical analysis was carried out by IR and NMR spectroscopy which gave the expected peaks and signals. Thin layer chromatography and comparison of melting points with literature data confirmed the purity of the products **3**.

References: J. Schmeyers, F. Toda, J. Boy, G. Kaupp, *J. Chem. Soc., Perkin Trans. 2*, 989 (1998); *J. Chem. Soc., Perkin Trans. 2*, 132 (2001).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: primary amine, carbonyl compound, gas-solid reaction, *N*-alkyl-azomethine

**Experimental procedures:**

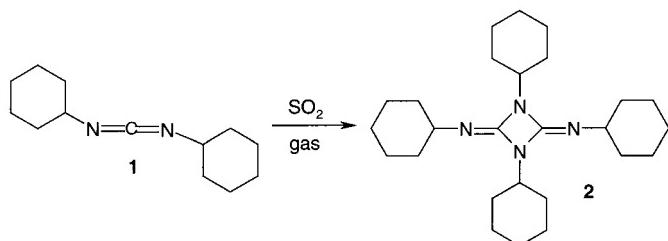
1 mmol of the crystalline aromatic aldehyde **1** in an evacuated 50-mL round-bottomed flask were treated with 1 bar of methyl- or ethylamine over night at room temperature. For **1b** 100 mL, 0.25 bar and 0 °C were applied. Excess gas was condensed to a receiver at –196 °C. The water of reaction was removed from the crystals at 0.01 bar and 80 °C. The purity of the weighed products (100% yield) was checked by mp and ^1H and ^{13}C NMR.

References: G. Kaupp, J. Schmeyers, J. Boy, *Tetrahedron*, **56**, 6899 (2000).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: dicyclohexylcarbodiimide, [2+2]-cycloaddition, catalysis, waste-free, gas-solid reaction



Experimental procedure:

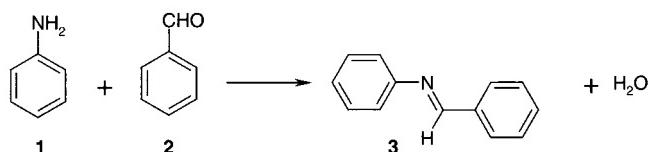
Crystals of dicyclohexylcarbodiimide **1** (1.00 g, 4.8 mmol) were exposed to SO_2 (1 bar) in a 500-mL flask at 0 °C for 21 h. The catalyst gas was pumped off and a quantitative yield of the dimer **2** was obtained (mp 115–118 °C). The purity was verified by various spectroscopic techniques.

References: G. Kaupp, D. Lübben, O. Sauerland, *Phosphorus, Sulfur, and Silicon*, **53**, 109 (1990).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: aniline, benzaldehyde, large scale, condensation, waste-free, azomethine



Experimental procedures:

A flat steel pan (31×44 cm²) was charged with benzaldehyde **2** (99.5%, 848 g, 7.95 mol) and aniline **1** (99.5%, 744 g, 7.95 mol). The liquids were mixed at 18 °C. The temperature rose to a maximum of 32 °C and fell back to 24 °C when crystallization started with another increase in temperature to a maximum of 35 °C within 12 min when crystallization was virtually complete and water of reaction separated. Next day, the wet crystal cake was crunched with an ordinary

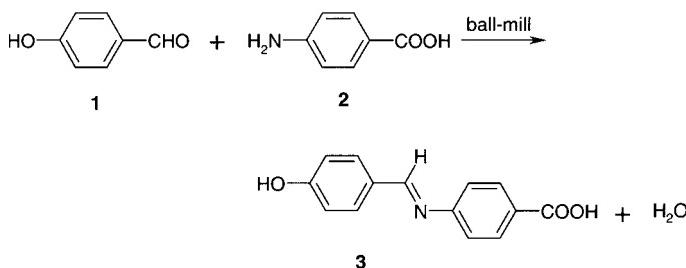
house-hold grain-mill and dried in a vacuum at room temperature to give 1.438 kg (100%) of pure benzylidene-aniline **3**.

References: G. Kaupp, *Angew. Chem.*, **113**, 4640 (2001); *Angew. Chem. Int. Ed. Engl.*, **40**, 4508 (2001); G. Kaupp, *Chryst. Eng. Comm.*, **8**, 797 (2006); G. Kaupp, *J. Phys. Org. Chem.*, **21**, 630 (2008).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: *p*-hydroxybenzaldehyde, *p*-amino benzoic acid, condensation, large scale, ball-mill, waste-free, solid-solid reaction, azomethine



Experimental procedure:

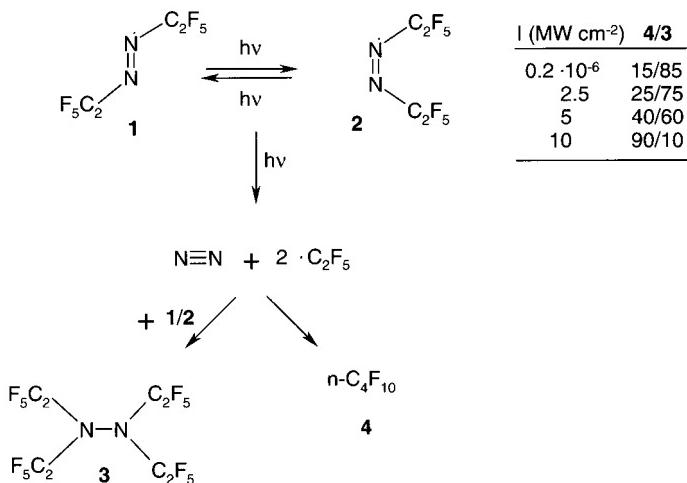
200 g quantities of a stoichiometric 1:1-mixture of the loosely premixed commercial crystals of **1** and **2**, both at >99% purity, were fed to a stainless-steel 2-L horizontal ball-mill (Simoloyer®) equipped with a hard-metal rotor, steel balls (2 kg; 100Cr6; 5 mm diameter) and water cooling. The temperature was 15 °C at the walls with a maximum of 19 °C in the center of the mill. The rotor was run at 900 min⁻¹ (the power was 610 W) for 15 min for quantitative reaction. 100% conversion and 100% yield was indicated by mp, IR spectrum, chemical analyses and DSC experiments. The product **3**·H₂O was milled out for 10 min leaving some holdup, but a quantitative recovery was obtained from the second batch and so on. For quantitative recovery of the powdered material in the last batch, an internal air cycle for deposition through a cyclone should be used. The hydrate water was removed from **3**·H₂O by heating to 80 °C in a vacuum.

References: G. Kaupp, J. Schmeyers, M. R. Naimi-Jamal, H. Zoz, H. Ren, *Chem. Engin. Sci.*, **57**, 763 (2002).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: elimination, trapping, radicals, isomerization, laser photochemistry

**Experimental procedure:**

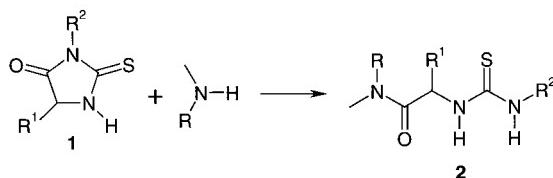
Samples of **1** (200 mg) were sealed in evacuated Pyrex ampoules (inner diameter 4 mm) and immersed in a 500-mL Pyrex beaker filled with ice and water in such a way that no ice blocked the laser beam. The beam of an excimer laser (Lambda Physics, EMC 201; XeCl; 17 ns pulses; 50 Hz repetition rate; 3 h; $\lambda = 308 \text{ nm}$) was positioned vertically using two dielectric mirrors and focused to the desired intensity by a quartz-lens with a focal length of 20 cm. For low intensity irradiations, the ampoules were placed in front of a mercury arc at a distance of 5 cm. The product ratio depended on the light intensity. The compounds **1**, **2**, **3** and **4** were separated by gas chromatography or HPLC on RP18 and spectroscopically characterized after 93–97% conversion to **3** and **4**.

References: G. Kaupp, O. Sauerland, *J. Photochem. Photobiol. A: Chem.*, **56**, 375 (1991).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: thiohydantoin, amine, ring opening, waste-free, gas-solid reaction, thioureido-acetamide



- a: R¹=R²=H
- b: R¹=R²=H, R=CH₃
- c: R¹=R=H, R²=Ph
- d: R¹=H, R²=Ph, R=CH₃
- e: R¹=CH₂Ph, R²=R=H
- f: R¹=CH₂Ph, R²=H, R=CH₃

Experimental procedures:

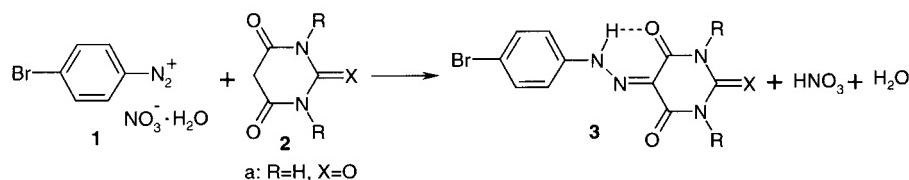
The thiohydantoin crystals **1a–f** (2.0 mmol) were treated with the gaseous amine (1 bar) at room temperature in an evacuated 500-mL flask through a vacuum line. After standing for about 12 h the excess gas was pumped off. The yield of solid **2a–f** was 100% in all cases.

References: G. Kaupp, J. Schmeyers, *Angew. Chem.*, **105**, 1656 (1993); *Angew. Chem. Int. Ed. Engl.*, **32**, 1587 (1993).

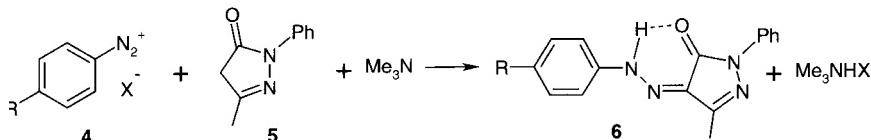
Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: solid diazonium salt, barbituric acid, pyrazolinone, azocoupling, solid-solid reaction, hydrazone structure



- a: R=H, X=O
- b: R=Me, X=O
- c: R=Et, X=O
- d: R=Ph, X=O
- e: R=Et, X=S



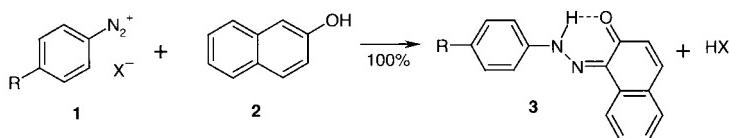
- a: R=NO₂, X=BF₄⁻
- b: R=OMe, X=NO₃⁻
- c: R=Br, X=NO₃⁻·H₂O
- d: R=NO₂, X=Cl⁻

Experimental procedures:**Caution: solid diazonium salts are heat- and shock-sensitive; do not ball-mill!**

3: The barbituric acid derivative **2** (0.50 mmol) was ground in an agate mortar. Solid diazonium salt **1** (0.50 mmol) was added and co-ground in 5 portions for 5 min, each. Most of the diazonium band at 2280 cm^{-1} had disappeared, but completion of the reaction was achieved by 24 h ultrasound application in a test tube. After neutralization (0.5 n NaOH, 20 mL), washings (H_2O) and drying, the quantitatively obtained products **3a–e** assume the hydrazone structure.

6: The pyrazolone **5** (1.00 mmol) and the solid diazonium salt **4** (1.00 mmol) were cautiously co-ground in an agate mortar for 5 min. The mixture was transferred to a 100 mL flask which was then evacuated. Me_3N (0.5 bar) was let in. After 12 h at room temperature, excess gas was recovered in a remote trap at -196°C . The salt was washed away with water (20 mL) and the residual solid dried. The yield was 98–99% of pure **6a–d** with the hydrazone structure.

Reference: G. Kaupp, A. Herrmann, J. Schmeyers, *Chem. Eur. J.*, **8**, 1395 (2002).

Type of reaction: C–N bond formation**Reaction condition:** solid-state**Keywords:** solid diazonium salt, β -naphthol, azocoupling, solid-solid reaction, hydrazone structurea: R= NO_2 , X= BF_4^- b: R=H, X= NO_2^- c: R=Cl, X= $\text{NO}_3^- \cdot \text{H}_2\text{O}$ d: R=Br, X= $\text{NO}_3^- \cdot \text{H}_2\text{O}$ **Experimental procedures:****Caution: these reactions might occur violently; use smooth agate mortar and do not ball-mill!**

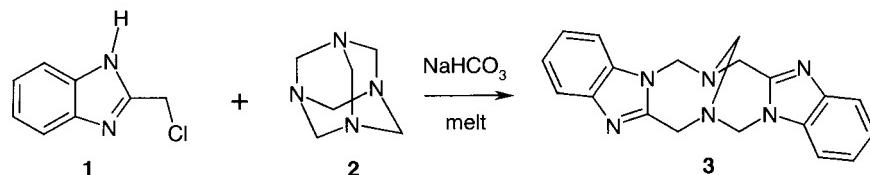
Solid diazonium salt **1** (0.50 mmol) and β -naphthol **2** (0.60 mmol) were separately ground in agate mortars and cautiously mixed. In the case of **1d** $\text{MgSO}_4 \cdot 2\text{H}_2\text{O}$ (0.50 mmol) was added to the mixture. The mixtures rested for 24 h in test tubes and were then exposed to ultrasound for 24 h in a cleaning bath. The quantitatively obtained “azo-dye” salts **3·HX** were neutralized and freed from excess **2** by washings with 0.5 n NaOH (20 mL) and water (20 mL). The yields of the neutral dyes with the hydrazone structure **3a–d** were 100, 98, 99 and 99%.

References: G. Kaupp, A. Herrmann, J. Schmeyers, *Chem. Eur. J.*, **8**, 1395 (2002).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: chloromethylbenzimidazole, urotropin, multimethylation, melt reaction, hexaazapoly[2.2.2]cycle



Experimental procedure:

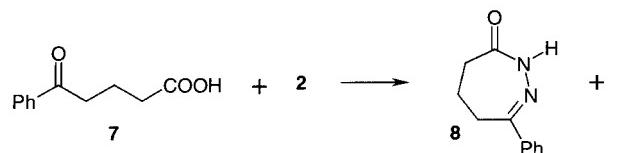
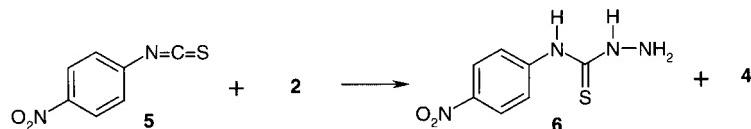
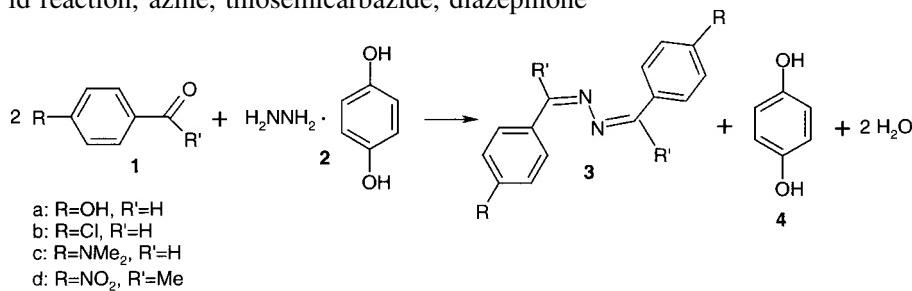
2-Chloromethylbenzimidazole **1** (1.66 g, 10.0 mmol), hexamethylenetetramine **2** (1.40 g, 10.0 mmol) and NaHCO₃ (1.00 g, 11.9 mmol) were mixed under argon and the melt heated within 5 min from 120°C to 160°C. The raw material was extracted with CH₂Cl₂ (to remove excess **2** and other impurities) and water (to remove the salts). The dried residue was pure **3** (0.92 g, 56%) with mp 226°C.

References: G. Kaupp, K. Sailer, *J. Prakt. Chem.*, **338**, 47 (1996).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: aldehyde, hydrazine, hydroquinone, ketone, isothiocyanate, solid-solid reaction, azine, thiosemicarbazide, diazepinone



Experimental procedures:

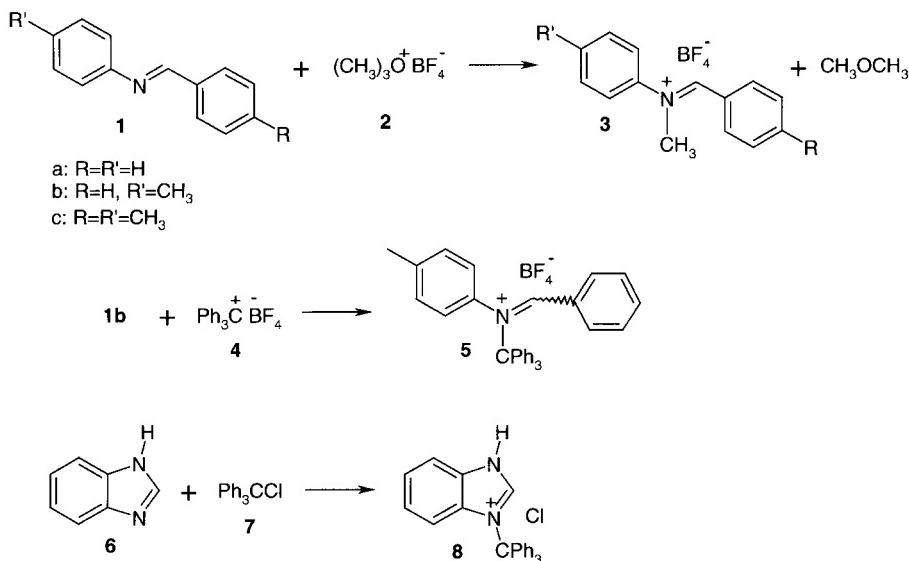
The aldehyde/ketone **1** (4.00 mmol), or the ketone **7** (2.00 mmol), or the isothiocyanate **5** (2.00 mmol) was ball-milled with the solid hydrazine-hydroquinone complex **2** (2.00 mmol) at 25–30 °C for 1 h (3 h in the case of **1d**). The yield was quantitative in all cases, as spectroscopically pure mixtures of **3**, **6**, **8** with **4** were obtained. Hydroquinone **4** was removed by 5 min trituration with 20 mL of water, filtration and three washings with 2 mL of water, each. The residue was dried in a vacuum to obtain the pure products. **4** was recycled from the aqueous washings by evaporation, addition of 1.0 g of 80% hydrazine hydrate in water per 4 mmol of initially reacted **2** and recrystallization to give 520 mg (91%) of pure **2** after filtration, washing with water and drying.

References: G. Kaupp, J. Schmeyers, *J. Phys. Org. Chem.*, **13**, 388 (2000).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: imines, carbocation, oxonium salt, quaternary salts, waste-free, solid-solid reaction, iminium salts

**Experimental procedures:**

Precisely weighed samples of **2** (ca. 2 mmol), or **4** (ca. 1 mmol), or **7** (1.00 mmol) were placed in a ball mill under argon together with the precise equivalent of **1a–c**, or **1b**, or **6**, respectively. The Teflon gasket was closed with

a torque of 50 Nm and ball-milling started for 1 h. The deliquescent salts **3**, **5**, **8** were quantitatively obtained and collected and stored under dry argon.

References: G. Kaupp, J. Schmeyers, J. Boy, *J. Prakt. Chem.*, **342**, 269 (2000).

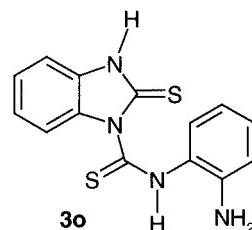
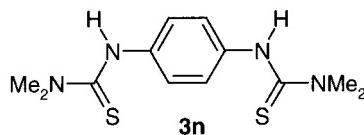
Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: isothiocyanates, amines, waste-free, gas-solid reaction, solid-solid reaction, thiourea



R	R'/R''	T(°C)	
a: Ph	H/H	-30	gs
b: 4-BrC ₆ H ₄	Me/H	rt	gs
c: 4-Br C ₆ H ₄	Me/Me	rt	gs
d: 1-Naph	Me/H	rt	gs
e: 1-Naph	Me/Me	rt	gs
f: 4-NO ₂ C ₆ H ₄	Me/H	rt	gs
g: 4-NO ₂ C ₆ H ₄	Me/Me	rt	gs
h: Me	H/H	0	gs
i: Me	Me/H	0	gs
j: Me	Me/Me	0	gs
k: Me	4-MeOC ₆ H ₄ /H	rt	mo
l: Me	4-Br C ₆ H ₄ /H	rt	mo
m: Me	4-Cl C ₆ H ₄ /H	rt	mo
n: 4-S=C=N-C ₆ H ₄	Me/Me	rt	gs
o: 2-S=C=N-C ₆ H ₄	2-NH ₂ C ₆ H ₄ /H	rt	bm



Experimental procedures:

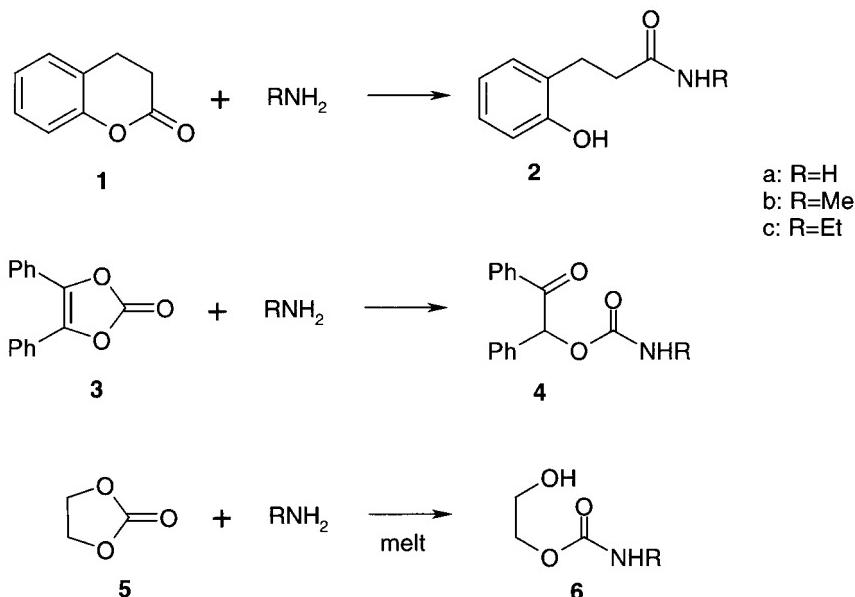
Crystalline isothiocyanates **1** (gs: 2.00 mmol, 1 bar of **2**, 250-mL flask, overnight; mo: 2.00 mmol, stoichiometric mixture, grinding in a mortar, standing for 1 day, intermediate softening; bm: 1 h ball-milling of stoichiometric mixture of **10** and *o*-phenylenediamine) were, depending on the melting points and eutectica, reacted with the amine gases **2** (1 bar) or with the solid anilines **2** (2.00 mmol). Excess gas was recovered by condensation at -196 °C. The yields were 100% in all cases.

References: G. Kaupp, J. Schmeyers, J. Boy, *Tetrahedron*, **56**, 6899 (2000).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: lactone, carbonic ester, amine, ring opening, waste-free, gas-solid reaction, amide, carbamate



Experimental procedures:

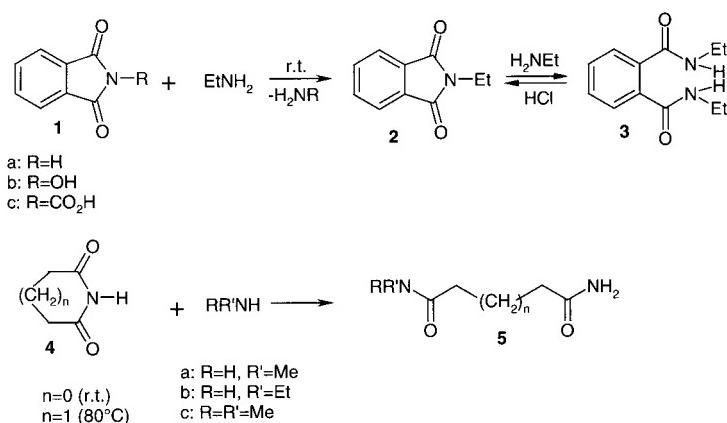
Compound **1** (2.00 mmol, 0 °C, overnight), **3** (2.00 mmol, rt, 1 day), or **5** (7.5 mmol, rt, 1 h, liquefies) in evacuated 250-mL flasks were treated with 0.8 bar ammonia, or methylamine, or ethylamine (**1** and EtNH_2 at 0.2 bar). Excess gas was recovered by condensation at –196 °C. The products **2** and **4** were quantitatively obtained. The liquid products **6** were isolated by distillation in 92, 93 and 92% yield.

References: G. Kaupp, J. Schmeyers, J. Boy, *Tetrahedron*, **56**, 6899 (2000).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: imides, amines, ring opening, cyclization, gas-solid reaction, diamides



Experimental procedures:

3: The phthalimides **1** (2.00 mmol) were reacted in 500-mL flasks with EtNH₂ (0.8 bar, 17.8 mmol) overnight. Excess gas and H₂NR were recovered in a cold trap at -196 °C. Glycine, in the case of **1c**, was washed away with water. Compound **3** was quantitatively obtained in all cases.

2: The diamide **3** (1.00 mmol) was exposed to HCl (1 bar) at room temperature overnight. Ethylammonium chloride was washed away with water and the imide **2** was quantitatively obtained after drying.

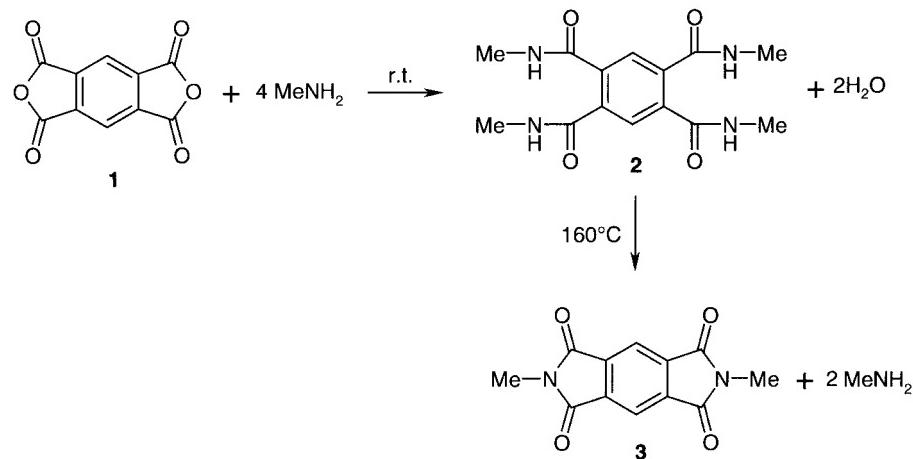
5: Crystals of succinimide or glutarimide (200 mg, 2.02 or 1.77 mmol) in an evacuated 500-mL flask were treated at room temperature or 80 °C with 1 bar or 0.8 bar, respectively, of methyl-, or ethyl-, or dimethylamine and left overnight or for 8 h, respectively. Excess gas was recovered in a -196 °C trap. The yield was quantitative in all cases.

References: G. Kaupp, J. Schmeyers, J. Boy, *Tetrahedron*, **56**, 6899 (2000).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: anhydride, methylamine, waste-free, gas-solid reaction, amides, cyclization, imide

**Experimental procedures:**

2: Pyromellitic dianhydride **1** (436 mg, 2.00 mmol) was placed in an evacuated 100-mL flask and treated with methylamine from a lecture bottle when the temperature rose to a maximum of 95°C for 2 min, but melting was avoided. For completion of the reaction, the flask (methylamine, 1 bar) was left overnight. Excess gas and water were evaporated to give a quantitative yield of pure **2**.

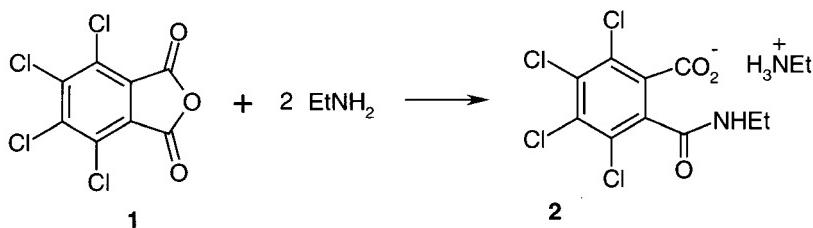
3: Pyromellitic tetramethylamide **2** (306 mg, 1.00 mmol) was heated to 160°C in an evacuated flask for 12 h with occasional evaporation. The pure diimide **3** was quantitatively obtained.

References: G. Kaupp, J. Schmeyers, J. Boy, *Tetrahedron*, **56**, 6899 (2000).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: large scale, anhydride, ethylamine, waste-free, gas-solid reaction, amides



Experimental procedures:

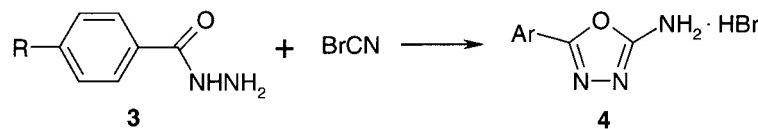
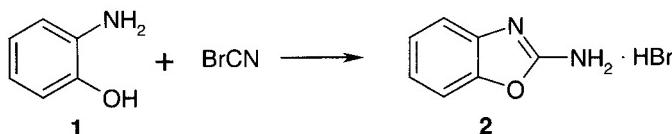
A 2-L flask with tetrachlorophthalic anhydride **1** (500 g) was evacuated at a tight rotatory evaporator. The rotating flask was immersed in a cooling bath at about 14 °C and ethylamine from a steel bottle was continuously let in by adjusting a pressure of 0.5–0.8 bar with a needle valve (while using a security valve under a hood for safety reasons). When the heat production had ceased after 8 h the conversion was ca. 75% and became very slow, due to the aggregation of the 40 µm grains to give 0.5–3 mm particles. After intermediate removal of the gas, the material was ground in a large mortar and the reaction with ethylamine continued at 50 °C for a quantitative yield.

References: G. Kaupp, J. Schmeyers, J. Boy, *Tetrahedron*, **56**, 6899 (2000); *Chemosphere*, **43**, 55 (2001).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: cyanogen bromide, 2-aminophenol hydrazide, cyclization, waste-free, gas-solid reaction, aminobenzoxazole, amino oxadiazole



a: R=H

b: R=CH₃

c: R=OH

Experimental procedures:

Solid **1** (10.0 mmol) was treated with BrCN (11.0 mmol) from a connected flask at a vacuum line. After standing overnight and recovering of the excess gas a quantitative yield of the aminobenzoxazole hydrobromide **2** was obtained.

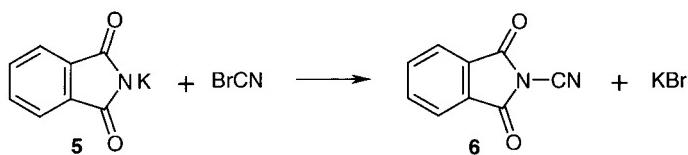
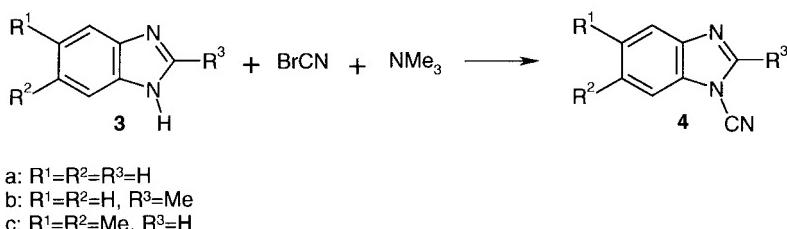
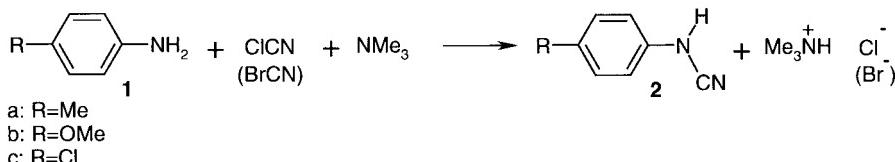
Similarly, the hydrazides **3a–c** (10 mmol) and BrCN (11.0 mmol) gave quantitative yields of **4a–c**.

References: G. Kaupp, J. Schmeyers, J. Boy, *Chem. Eur. J.*, **4**, 2467 (1998).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: cyanogen chloride, cyanogen bromide, amines, gas-solid reaction, cyanamides



Experimental procedures:

2 and 4: The crystalline substrate **1a–c** or **3a–c** (10 mmol) was placed in a 500-mL flask which was evacuated and filled with a 1:1-mixture of ClCN and trimethylamine (11.7 mmol, each), or it was placed in an evacuated 250-mL wide-neck flask connected to a 250-mL wide-neck flask with freshly sublimed BrCN (1.17 g, 11.0 mmol) and trimethylamine (0.5 bar, 11.7 mmol) was added through a vacuum line. A magnetic spin bar was rotated in the flask in order to mix the gases and the system was left overnight at room temperature. Excess gas was pumped to a cold trap at -196 °C. The trimethylammonium chloride (bromide) was removed by washings with water. The yield of **2** or **4** was quantitative in all cases.

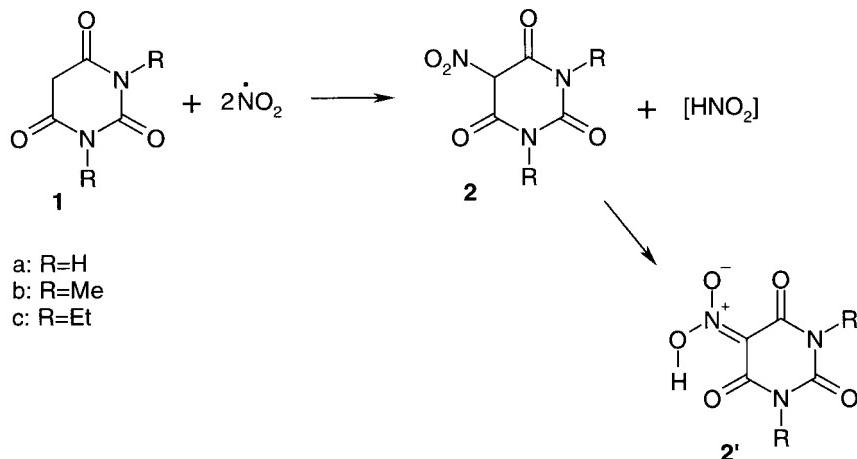
6: Potassium phthalimide **5** (370 mg, 2 mmol) was ball-milled to a particle size of <1 μm (30 min) and then treated with gaseous BrCN (225 mg, 2.10 mmol) for 24 h. Excess gas was pumped to a cold trap at -196 °C and KBr removed by washings with water. The yield of **6** was 340 mg (99%), mp 73 °C.

References: G. Kaupp, J. Schmeyers, J. Boy, *Chem. Eur. J.*, **4**, 2467 (1998).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: barbituric acid, nitrogen dioxide, nitration, waste-free, gas-solid reaction



Experimental procedures:

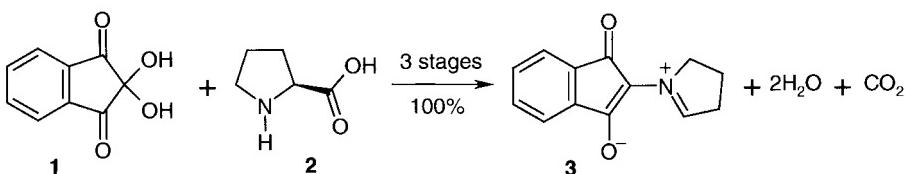
Barbituric acid **1a** (500 mg, 3.91 mmol) or **1b** (500 mg, 3.21 mmol), or **1c** (500 mg, 2.72 mmol) in an evacuated flask was treated with NO_2 (6.4 mmol) at an initial pressure of 0.3 bar for 4 h. After condensation of the gases to a cold trap at -196°C and drying of the solid products at 80°C in a vacuum the pure compounds **2a–c**, that assume the aci-nitro form **2'**, were quantitatively obtained.

References: G. Kaupp, J. Schmeyers, *J. Org. Chem.*, **60**, 5494 (1995).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: large scale, ninhydrin, L-proline, cascade reaction, zwitterion, waste-free, solid-solid reaction



Experimental procedure:

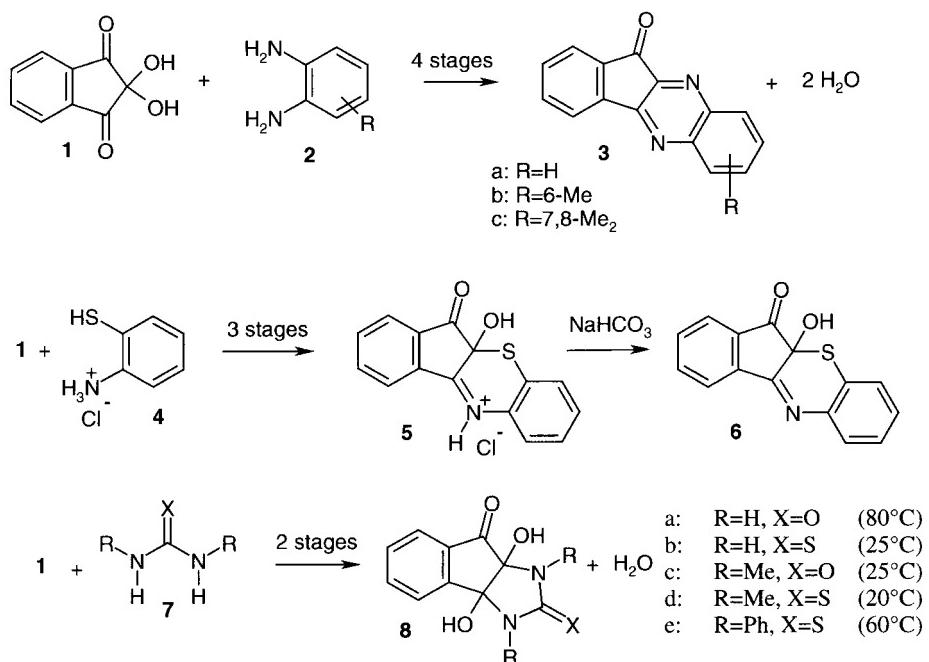
A stoichiometric mixture of ninhydrin and L-proline **2** (200 g) was milled in a 2-L horizontal ball-mill (Simoloyer®) with steel balls (100Cr6, 2 kg, diameter 5 mm) at 1100 min⁻¹ for 40 min until the liberation of CO₂ was complete. The temperature varied from 15 °C at the water cooled walls to 21 °C in the center. The power was 800 W. Quantitative reaction to give **3** was secured by weight (146 g, 100%) and by spectroscopic techniques. The product was not separated in a cyclone but the milling-out towards the end was completed with 4 times 250 mL of water, each. This part of the highly disperse (<1 μm) pure azomethine ylide **3** was obtained after centrifugation and drying in a vacuum. The combined water phase contained 0.2 g of **3**.

References: G. Kaupp, M.R. Naimi-Jamel, H. Ren, H. Zoz, *Chemie Technik*, **31**, 58 (2002).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: ninhydrin, *o*-phenylenediamine, *o*-aminothiophenol hydrochloride, (thio)urea, cascade reaction, solid-solid reaction



Experimental procedures:

Preparation of 3a: Ninhhydrin **1** (356 mg, 2.00 mmol) and *o*-phenylenediamine **2a** (216 mg, 2.00 mmol) were ball-milled for 15 min at –5 °C. Compound **3a** (461 mg, 99%) was obtained after drying in a vacuum at 80 °C. Mp 217–218 °C. Similarly, the compounds **3b–c** were quantitatively obtained.

Preparation of 5, 6: Ninhhydrin **1** (356 mg, 2.00 mmol) and *o*-aminothiophenol hydrochloride (**4**) (323 mg, 2.00 mmol) were ball-milled for 1 h. The solid salt **5** was triturated with saturated NaHCO₃ solution, washed with water and dried to obtain pure **6** (529 mg, 99%). Mp 227 °C.

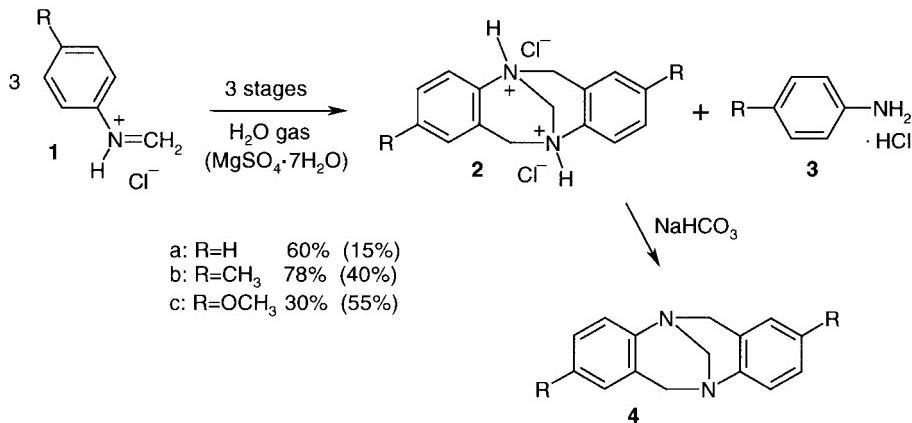
Preparation of 8a: Ninhhydrin **1** (534 mg, 3.00 mmol) and urea **7a** (180 mg, 3.00 mmol) were ball-milled at 80 °C for 1 h. After drying at 140 °C in a vacuum for 5 min pure **8a** (696 mg, 100%) was obtained. Mp 218 °C (decomposition). The compounds **8b–e** were similarly obtained in quantitative yield by ball-milling at the temperatures given.

References: G. Kaupp, M.R. Naimi-Jamal, J. Schmeyers, *Chem. Eur. J.*, **8**, 594 (2002).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: *N*-arylmethylenimine, cascade reaction, solid-solid reaction, gas-solid reaction, aminomethylation, cyclization, Troeger base, 1,3,5-triarylhexahydrotriazine



Experimental procedures:

Gas-solid reaction: The methyleniminium chloride **1a–c** (2.0 mmol) – from gas-solid reaction of the 1,3,5-triarylhexahydrotriazine with HCl – was ball-milled for 5 min and then spread on a watch glass with 15 cm diameter in air of 35%

relative humidity at about 22 °C. The characteristic IR-bands of the C=N group of **1a–c** had disappeared after 1 h when the material became deliquescent. The stoichiometric 1:1 mixtures of **2** and **3** and polymerized products were separated by chromatography after washings with NaHCO₃ solution to obtain **4a–c** with the yields indicated.

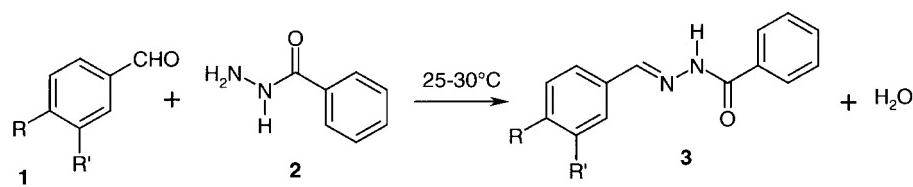
Solid-solid reaction: The methyleniminium chloride **1a–c** (1.0 g) and MgSO₄·7H₂O (10 g) as a solid water-supply were co-ground in a mortar for 10 min. The solid mixture was extracted with CH₂Cl₂ (30 mL, 5 times with centrifugation) and the Troeger base **4a,b,c** separated by chromatography.

References: G. Kaupp, J. Schmeyers, J. Boy, *J. Prakt. Chem.*, **342**, 269 (2000).

Type of reaction: C–N bond formation

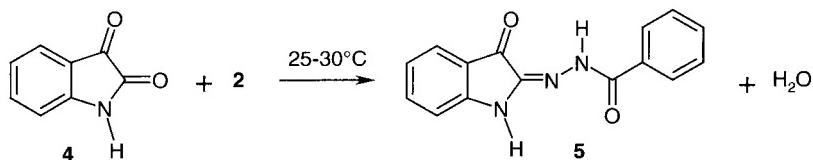
Reaction condition: solid-state

Keywords: solid benzaldehydes, benzhydrazide, isatin, waste-free, solid-solid reaction, acyl hydrazide



a: R=OH, R'=H

b: R=H, R'=NO₂



Experimental procedures:

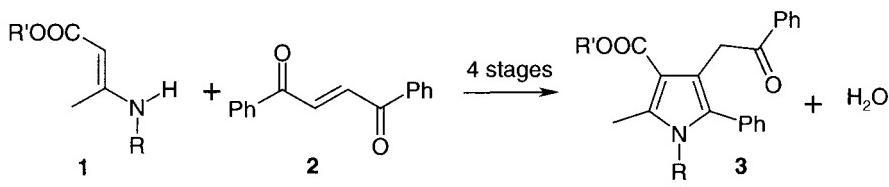
The aldehydes **1** (2.00 mmol) or isatin **4** (2.00 mmol) and benzhydrazide **2** (272 mg, 2.00 mmol) were ball-milled at 25–30 °C for 1 h or 3 h, respectively. After drying at 0.01 bar at 80 °C **3a,b** or **5** were obtained in pure form with quantitative yield.

References: G. Kaupp, J. Schmeyers, J. Boy, *J. Prakt. Chem.*, **342**, 269 (2000).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: enamine, dibenzoylethene, cyclization, cascade reaction, waste-free, solid-solid reaction, pyrrole

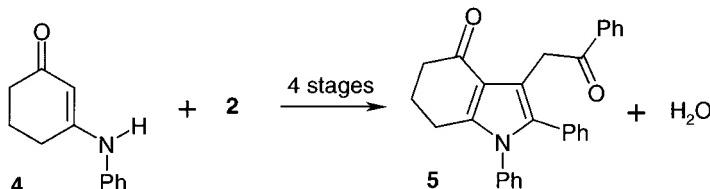


a: R=H, R'=CH₃

b: R=R'=CH₃

c: R=CH₃, R'=C₂H₅

d: R=CH₂Ph, R'=C₂H₅



Experimental procedures:

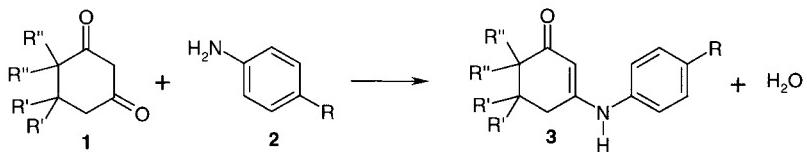
A ball-mill (Retsch MM 2000) with a 10-mL beaker out of stainless steel and two steel balls (6.5 g) was run at 20–30 Hz for 3 h in order to achieve quantitative conversions from stoichiometric mixtures of **1** or **4** and **2**. Milling of **1a–d** or **4** (2.00 mmol) and **2** (2.00 mmol) gave dust-dry powders of **3a,b,d** or **5** in quantitative yield that were heated to 80 °C for removal of the water of reaction. Compound **3c** had to be heated to 150 °C for 5 min in order to complete the elimination of water from its direct precursor. Solution reactions, at 65 °C (3 h) gave inferior yields.

References: G. Kaupp, J. Schmeyers, A. Kuse, A. Atfeh, *Angew. Chem.*, **111**, 3073 (1999); *Angew. Chem. Int. Ed. Engl.*, **38**, 2896 (1999).

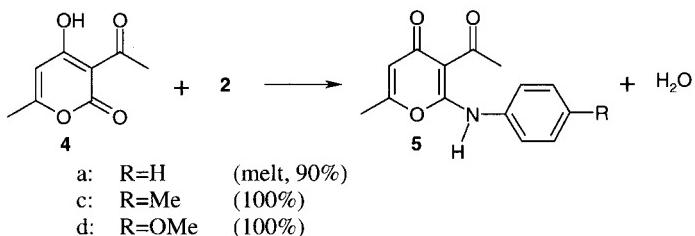
Type of reaction: C–N bond formation

Reaction condition: solid-state, solvent-free

Keywords: 1,3-cyclohexanedione, anilines, melt-reaction, solid-solid reaction, enamine ketone



- a: R=R'=R''=H (melt, 85%)
- b: R=H, R'=Me, R''=H (melt, 100%)
- c: R=Me, R'=R''=H (100%)
- d: R=OMe, R'=R''=H (100%)
- e: R=Cl, R'=R''=H (100%)
- f: R=R'=Me, R''=H (100%)
- g: R=OMe, R'=Me, R''=H (100%)
- h: R=Cl, R'=H, R''=Me (100%)



Experimental procedures:

Melt reactions: 2.00 mmol of the 1,3-dicarbonyl compound **1** or **4** and aniline (186 mg, 2.00 mmol) were heated to 80 °C for 1 h in an evacuated 50-mL flask in a drying oven. The solid product was dried at 0.01 bar at 80 °C. **1a** and **5a** were purified by recrystallization.

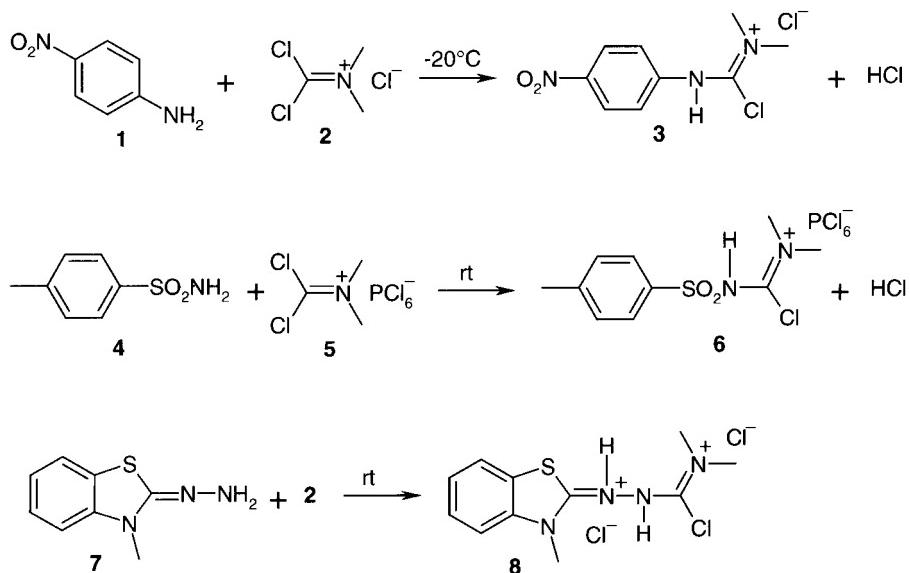
Solid-solid reactions: 2.00 mmol of the 1,3-dicarbonyl compound **1** or **4** and 2.00 mmol of the solid aniline derivative **2** were ball-milled at room temperature for 30 min. After drying of the solid hydrates at 0.01 bar at 80 °C the pure enamine ketones **3** or **5** were obtained with quantitative yield.

References: G. Kaupp, J. Schmeyers, J. Boy, *J. Prakt. Chem.*, **342**, 269 (2000).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: Viehe salt, nitroaniline, sulfonamide, hydrazone, solid-solid reaction



Experimental procedures:

Solid *p*-nitroaniline (690 mg, 5.00 mmol) and Viehe salt **2** (815 mg, 5.00 mmol) were ball-milled at -20 °C for 1 h. Most of the HCl escaped through the Teflon gasket that was tightened against a torque of 50 Nm. Residual HCl was pumped off at room temperature. The yield of pure salt **3** was 1.321 g (100%).

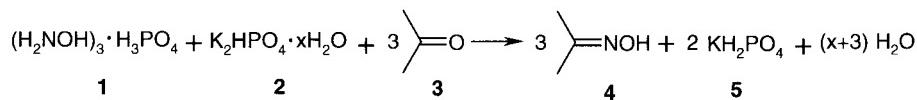
Compound **6** and **8** were quantitatively obtained by similar ball-milling of the appropriate components at room temperature.

References: G. Kaupp, J. Boy, J. Schmeyers, *J. Prakt. Chem.*, **340**, 346 (1998).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: hydroxylamine phosphate, acetone, large scale, exhaust gas purification, flow system, gas-solid reaction, acetone oxime



Experimental procedures:

Two heatable glass tubes ($l=50$ cm, i.d.=2 cm) fitted with glass frits were each loaded with 53.1 g (0.269 mol) of ground ($0.14 \text{ m}^2 \text{ g}^{-1}$) hydroxylaminium phosphate **1** and 51.9 g (0.269 mol) of un-ground ($0.10 \text{ m}^2 \text{ g}^{-1}$) $\text{K}_2\text{HPO}_4 \cdot \text{H}_2\text{O}$ **2**. Both tubes were externally heated to 80 °C. Air (1 L min⁻¹) was passed through 46.9 g (0.807 mol) of acetone **3** and then over the solids from the top of the tubes. All of the acetone (at a load of 78 g m⁻³) had reacted within 10 h. Behind the second column was a condenser flask in an ice bath and a filter of activated carbon (5 g, 645 m² g⁻¹) to catch the last traces of free acetone oxime **4** which escaped condensation. The product **4** and the water of reaction and crystal water were continuously expelled in gaseous form from the columns and condensed out at 0 °C. Only after >75% conversion, acetone started to escape from the first column and the second column started to react (at <50 g m⁻³ acetone load, such escape started at >90% conversion). After passing all of the acetone, column 1 had reacted to 94% and column **2** to 6%. The condensate consisted of water (18.5 g, 96%) and of crystalline acetone oxime **4** (58.7 g, 99.3%). The missing 400 mg (0.7%) of noncondensed **4** were efficiently and completely absorbed by the activated carbon at the exhaust (400 mg of **4** are absorbed by 3 g of activated carbon). The acetone oxime **4** was separated from water by continuous azeotropic removal with *tert*-butyl methyl ether. The reacted column was contracted by less than 10% and contained crystalline KH_2PO_4 **5** in analytically pure form as a couple product.

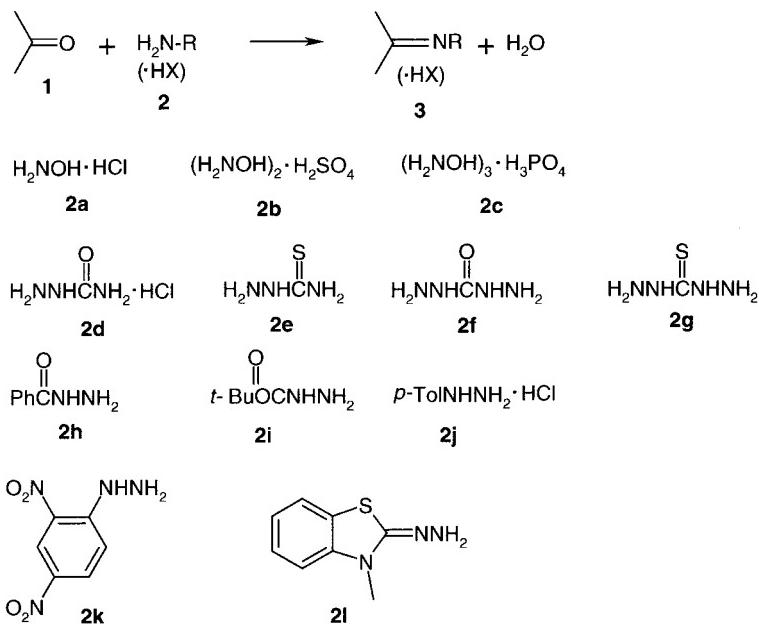
Apart from the quantitative synthesis of **4**, this experiment simulated an exhaust gas purification down to zero emission.

References: G. Kaupp, U. Pogodda, J. Schmeyers, *Chem. Ber.*, **127**, 2249 (1994).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: carbonyl reagent, acetone, hydroxyl amine, semicarbazide, hydrazine, condensation, waste-free, gas-solid reaction, imine



Experimental procedures:

Semicarbazide hydrochloride **2d** (1.00 g, 9.0 mmol) in an evacuated 1-L flask was connected with a vacuum line to a 100-mL flask containing 1.57 g (27 mmol) of degassed acetone **1**. After 12 h excess gas **1** and the water of the reaction were evaporated or condensed into the smaller flask. The yield of pure **3d** was 1.52 g (100%).

2,4-Dinitrophenylhydrazine **2k** (1.00 g, 5.1 mmol) was air dried from adhering water (which was there for safety reasons) with suction, placed in an evacuated 250-mL flask and connected with a vacuum line to a 100-mL flask which contained 0.58 g (10 mmol) of degassed acetone **1** and left overnight. Excess **1** and the water of the reaction were removed by evaporation. The yield of pure **3k** was 1.20 g (100%).

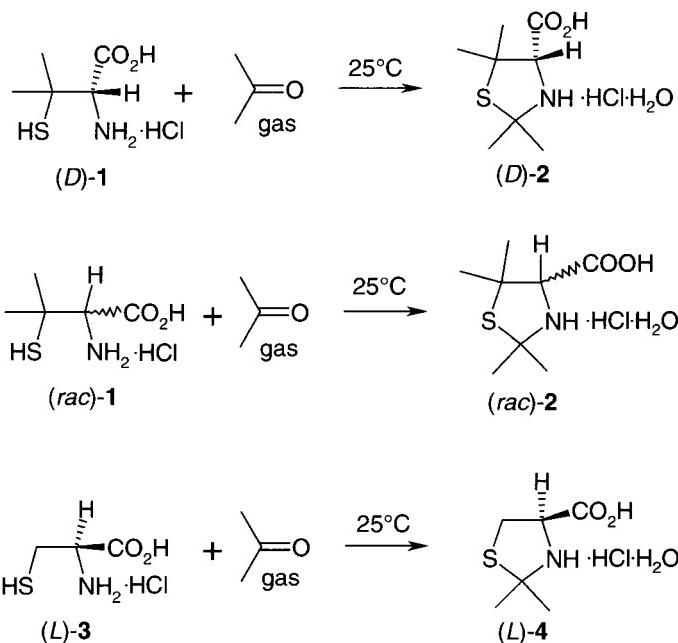
Similarly, all imines (imine salts) **3a–l** were obtained quantitatively. The reaction of **2a** provided a partially liquefied (deliquescent) **3a·HCl+H₂O** that lost the water and solidified upon evaporation. The reaction times with **2g** and **2l** were 2 and 3 days under these modest conditions.

References: G. Kaupp, U. Pogodda, J. Schmeyers, *Chem. Ber.*, **127**, 2249 (1994).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: penicillamine, acetone, cysteine, cyclization, gas-solid reaction, C–S bond formation, thiazolidine

**Experimental procedures:**

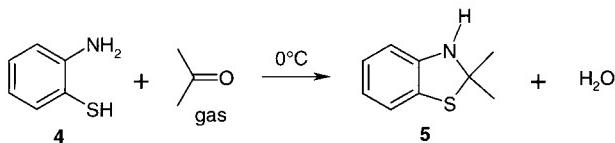
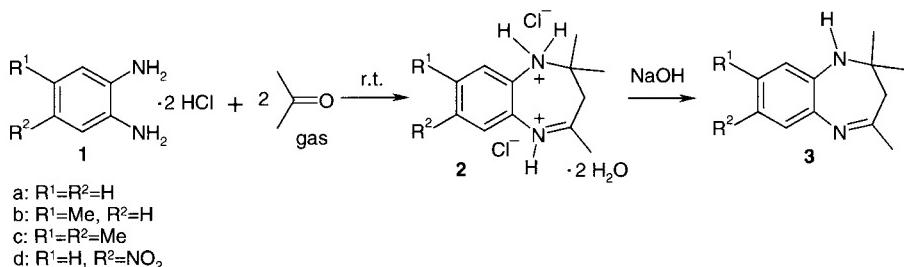
The hydrochlorides *D*-1, or *rac*-1, or *L*-3 (5.00 mmol) in an evacuated 50-mL flask were connected with a vacuum line to a 50-mL flask containing acetone (970 mg, 6.0 mmol). The acetone evaporated as it was consumed. After 12 h, excess gas was pumped off and a quantitative yield of the respective thiazolidine hydrochloride hydrate was obtained.

References: G. Kaupp, U. Pogodda, J. Schmeyers, *Chem. Ber.*, **127**, 2249 (1994).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: acetone, *o*-phenylenediamine, cyclization, cascade reaction, gas-solid reaction, benzodiazepine, benzothiazolidine



Experimental procedures:

The salt **1**·2HCl was quantitatively obtained from *o*-phenylenediamine and HCl gas at 0.5 bar in a flask that was rotating in an ice bath.

The salt **1**·2HCl (20 g, 80 mmol) was placed in a 10-L desiccator and after evacuation connected to a 100-mL flask containing 9.3–11.6 g (160–200 mmol) of acetone which had previously been degassed in a vacuum and cooled with liquid nitrogen. Upon removal of the cooling bath the acetone evaporated slowly into the desiccator. After 12 h, excess gas was condensed back to the flask (−196 °C) and a 100% yield of **2a**·2H₂O was obtained. The free base **3a** was liberated with NaOH in water.

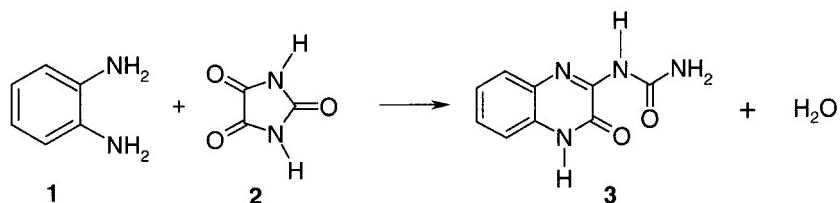
The reaction of **1d**·2HCl gave **2d**·2HCl·2H₂O (71%) and **3d** therefrom after neutralization. The reactions of **1b,c** and **4** (to give **5**) were performed with 1 g of the starting material. The yield was 100% in all cases.

References: G. Kaupp, U. Pogodda, J. Schmeyers, *Chem. Ber.*, **127**, 2249 (1994).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: *o*-phenylenediamine, parabanic acid, cyclization, cascade reaction, melt reaction, quinoxaline

**Experimental procedure:**

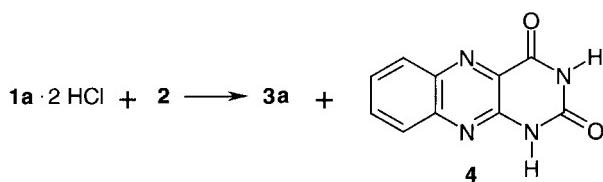
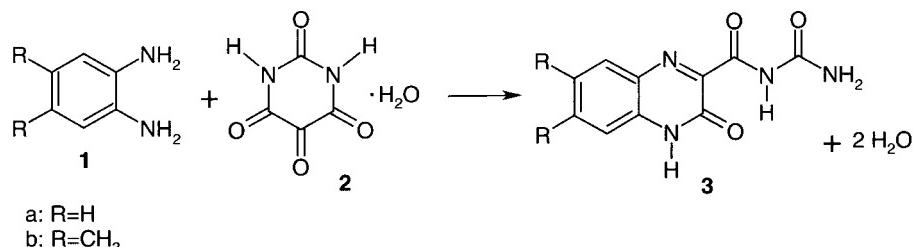
A melt of **1** (216 mg, 2.00 mmol) and parabanic acid **2** (228 mg, 2.00 mmol) was heated to 130–140 °C for 30 min in a vacuum. The raw material contained **3** (78%). It was washed with cold 50% AcOH (10 mL), and the residue was crystallized from AcOH to give 286 mg (70%) **3**.

References: G. Kaupp, M.R. Naimi-Jamal, *Eur. J. Org. Chem.*, 1368 (2002).

Type of reaction: C–N bond formation

Reaction condition: solid-state, solvent-free

Keywords: *o*-phenylenediamine, alloxane, cyclization, cascade reaction, solid-solid reaction, melt reaction, 2-quinoxalinone

**Experimental procedures:**

Crystalline *o*-phenylenediamine **1a** (108 mg, 1.00 mmol) and alloxane hydrate **2** (160 mg, 1.00 mmol) were ball-milled at room temperature for 1 h to give 232 mg (100%) of pure **3a**.

Similarly, a quantitative yield of **3b** was obtained.

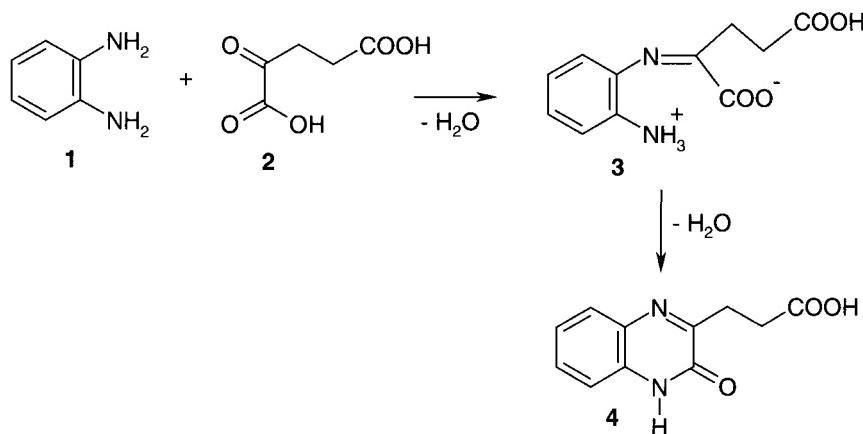
A stoichiometric melt of **1a·2HCl** and **2** was kept at 130–140 °C for 30 min. The mixture was heated with 20 mL of acetic acid when 14% **4** were filtered from the hot solution and 47% **3a** separated from the cold mother liquor.

References: G. Kaupp, M.R. Naimi-Jamal, *Eur. J. Org. Chem.*, 1368 (2002).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: *o*-phenylenediamine, 2-oxoglutaric acid, cyclization, cascade reaction, waste-free, solid-solid reaction, 2-quinoxalinone



Experimental procedure:

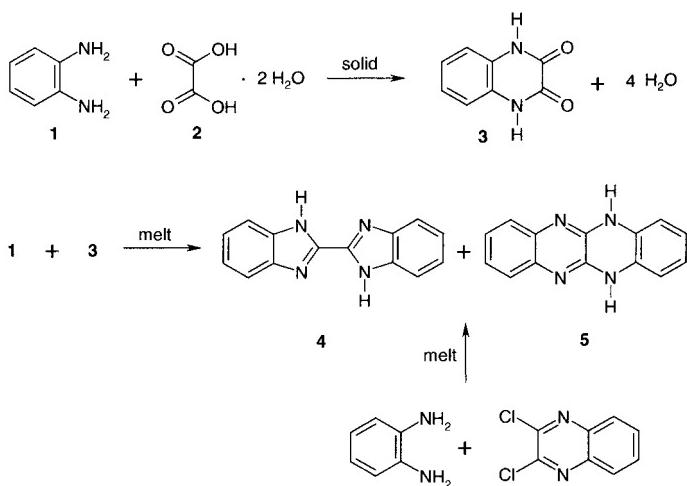
Crystalline *o*-phenylenediamine **1** (216 mg, 2.00 mmol) was co-ground in a mortar with 2-oxoglutaric acid **2** (242 mg, 2.00 mmol) and heated to 120–125 °C for 30 min in a vacuum. Pure **4** (472 mg, 100%) was obtained directly.

References: G. Kaupp, M.R. Naimi-Jamal, *Eur. J. Org. Chem.*, 1368 (2002).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: *o*-phenylenediamine, oxalic acid dihydrate, cyclization, quinoxalinedione, 2,3-dichloroquinoxaline, cascade reaction, solid-solid reaction, melt reaction, bis-benzimidazolyl, fluoflavin



Experimental procedures:

Crystalline *o*-phenylenediamine **1** (108 mg, 1.00 mmol) and oxalic acid dihydrate **2** (126 mg, 1.00 mmol) were co-ground in a mortar. The high melting salt was heated in a vacuum to 150 °C for 8 h, or to 180 °C for 30 min, or to 210–220 °C for 10 min. Pure **3** was obtained in all cases (162 mg, 100%).

The compounds **1** (54 mg, 0.50 mmol) and **3** (81 mg, 0.50 mmol) were heated to 240 °C for 12 h under vacuum. A crystalline 94:6-mixture of **4** and **5** was quantitatively obtained.

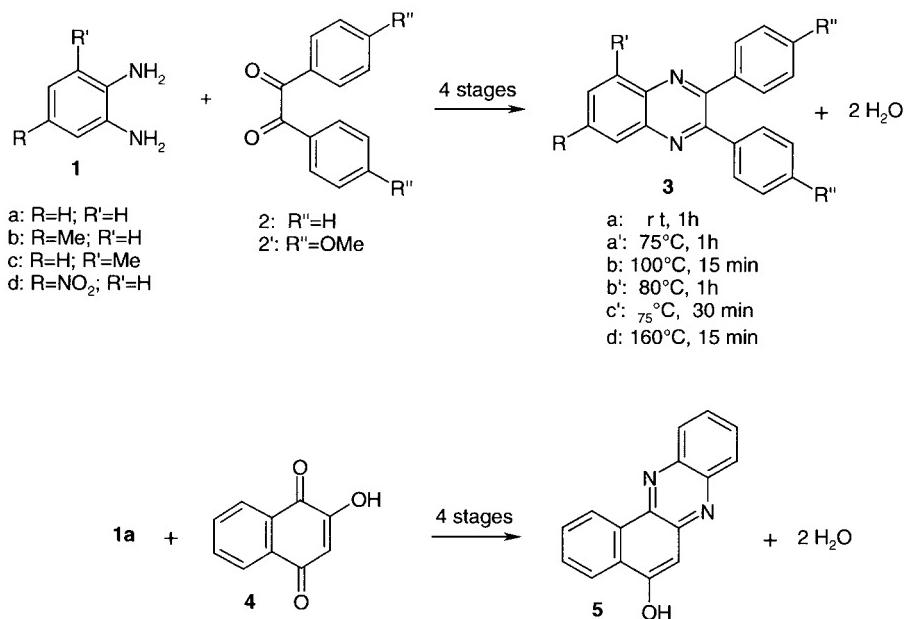
The compounds **1** (108 mg, 1.00 mmol) and 2,3-dichloroquinoxaline **6** (199 mg, 1.00 mmol) were heated to 150 °C in a vacuum for 30 min. The crude mixture contained 1·2HCl (39%), **4** (7%) and **5** (53%). After treatment with 1 n NaOH, water and cold ethanol (20 mL) the residue contained **5** and **4** in a 93:7 ratio. Pure fluoflavin **5** was obtained by heating the mixture with 5 mL of ethanol, hot filtration and three washings with 3 mL of hot ethanol.

References: G. Kaupp, M.R. Naimi-Jamal, Eur. J. Org. Chem., 1368 (2002).

Type of reaction: C–N bond formation

Reaction condition: solid-state, solvent-free

Keywords: *o*-phenylenediamine, benzil, cyclization, cascade reaction, melt reaction, waste-free, solid-solid reaction, quinoxaline



Experimental procedures:

Crystalline *o*-phenylenediamine **1a** (108 mg, 1.00 mmol) and benzil **2** (210 mg, 1.00 mmol) were ball-milled (heatable Retsch MM 2000, 10-mL steel beaker, two 12 mm balls, 20–25 Hz) for 1 h. Pure **3a** (282 mg, 100%) was obtained after removal of the water at 80 °C in a vacuum for 1 h.

Similarly, all the further products **3** were obtained with 100% yield at the temperatures given. **1b** and **1d** were co-ground with **2** at room temperature and heated in an oven for 15 min to 100 °C and 160 °C to obtain pure **3b** and **3d** with 100% yield.

Quantitative yields could also be obtained in stoichiometric melts at considerably higher temperatures in an evacuated 5-mL flask: **3a** at 100 °C, 20 min; **3a'** at 130 °C, 30 min; **3b'** at 130 °C, 30 min.

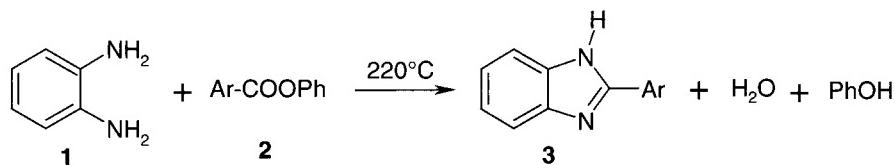
Compound **5** was similarly obtained with 100% yield in the solid state (70 °C, 15 min) and in the melt (110 °C, 30 min).

References: G. Kaupp, M.R. Naimi-Jamal, *Eur. J. Org. Chem.*, 1368 (2002).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: aryl ester, *o*-phenylenediamine, cyclization, melt reaction, benzimidazole



	Ar	yield (%)
a:	H	86
b:	<i>o</i> -OH	93
c:	<i>p</i> -OH	94
d:	<i>o</i> -Me	80
e:	<i>m</i> -Me	87
f:	<i>p</i> -Me	87
g:	<i>o</i> -Cl	87
h:	<i>p</i> -Cl	91
i:	<i>o</i> -NH ₂	45-60
j:	<i>p</i> -NH ₂	45-60

Experimental procedures:

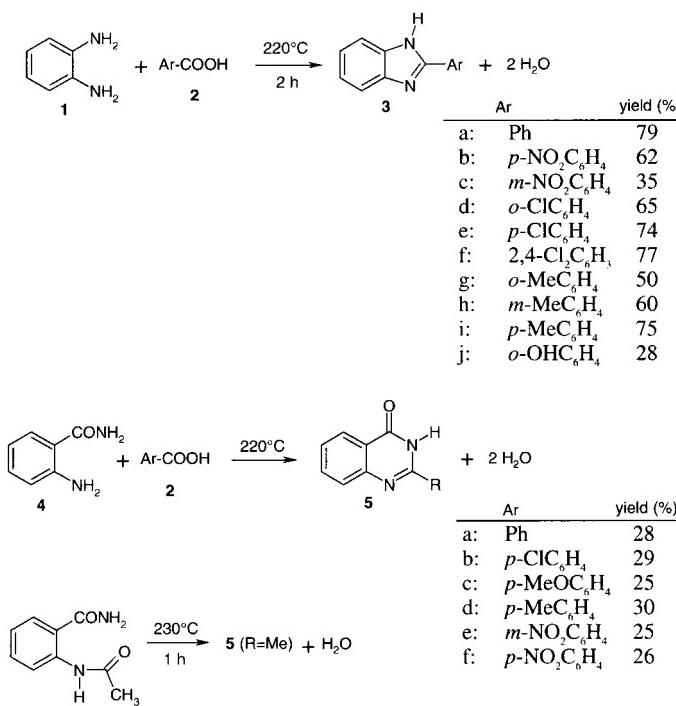
Stoichiometric mixtures of *o*-phenylenediamine **1** and (substituted) benzoic ester **2** were heated to 220°C for 1.5 h. The products **3** were isolated with the yields given.

References: T. Ebana, K. Yokota, Y. Takada, *Hokkaido Daigaku Kogakubu Kenkyu Hoku-ku*, **89**, 127–130 (1978), *Chem. Abstr.*, **91**, 157 660 (1979).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: 2-aminobenzamide, *o*-phenylenediamine, benzoic acid, ring closure, melt reaction, benzimidazole, quinazolinone



Experimental procedures:

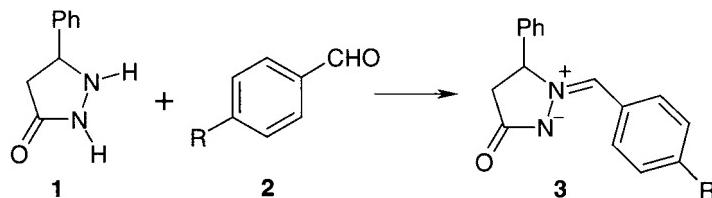
Mixtures of **1** and **2** were fused and kept at 180–220 °C for 1.5–2.5 h. The cooled solids were triturated with 10% aqueous NaHCO₃ to yield **3** in the yield indicated. The compounds **5** were similarly obtained at 220 °C for 4 h.

References: V.P. Reddy, P.L. Prasunamba, P.S.N. Reddy, C.V. Ratnam, *Indian J. Chem. Sect B.*, **22**, 917 (1983).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: pyrazolidinone, benzaldehyde, 1,3-dipol, uncatalyzed, azomethini-mine



- a: R=Cl
- b: R=Br
- c: R=NO₂

Experimental procedures:

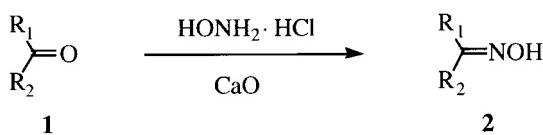
A stoichiometric mixture of **1** (5.00 mmol) and **2** (5.00 mmol) was co-ground in a mortar and heated to 80 °C for 1 h. The 1,3-dipol **3** crystallized from an intermediate melt and was obtained quantitatively in pure form: mp **3a**: 192 °C; **3b**: 210–211 °C; **3c**: 187–188 °C.

References: G. Kaupp, *CrystEngComm* **8**, 794 (2006), G. Kaupp, *Topics Curr. Chem.*, **254**, 95 (2005).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: aldehyde, ketone, calcium oxide, hydroxylamine hydrochloride, oxime



- a: R₁R₂=-(CH₂)₅-
 - b: R₁R₂=-(CH₂)₄-
 - c: R₁R₂=-(CH₂)₆-
 - d: R₁=R₂=Ph
 - e: R₁=Ph; R₂=Me
 - f: R₁=4-MeC₆H₄; R₂=H
 - g: R₁=3-MeC₆H₄; R₂=H
 - h: R₁=4-HOC₆H₄; R₂=H
 - i: R₁=2-HOC₆H₄; R₂=H
 - j: R₁=4-ClC₆H₄; R₂=H
 - k: R₁=3-ClC₆H₄; R₂=H
 - l: R₁=2,6-Cl₂C₆H₃; R₂=H

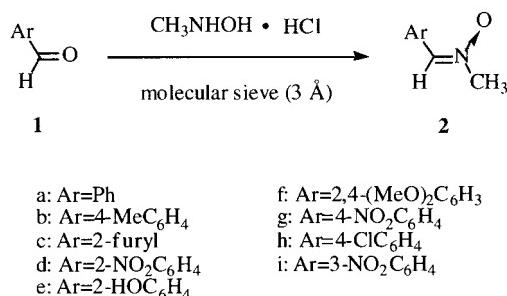
Experimental procedures:

A mixture of ketone or aldehyde (1 mmol), fine powder of CaO (0.5 g, 8.9 mmol) were heated in an oil bath for a few minutes. Then hydroxylamine hydrochloride (0.208 g, 3 mmol) was added and the mixture was stirred with a magnetic stirrer in the presence of air for appropriate time. Afterwards, the reaction mixture was mixed with ethylacetate, filtered to remove CaO then mixed with water and extracted. The ethylacetate solution was dried over Na_2SO_4 . The solvent was removed in vacuo to give the product.

References: H. Sharghi, M. H. Sarvari, *J. Chem. Res. (S)*, 24 (2000).

Type of reaction: C–N bond formation**Reaction condition:** solvent-free

Keywords: aromatic aldehyde, molecular sieve, condensation, α -aryl-*N*-methyl-nitrone

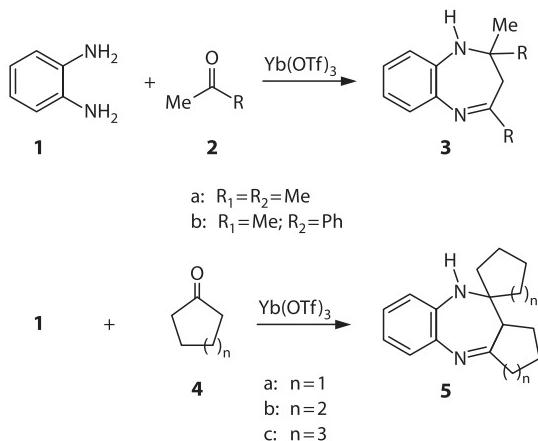
**Experimental procedures:**

A mixture of *N*-methylhydroxylamine hydrochloride (1.2 mmol), finely powdered molecular sieve (3 Å, 0.3 g), and benzaldehyde (1.2 mmol) were grinded thoroughly for 10 min. The reaction mixture was set aside for further 5 min at ambient temperature. To the crude product mixture, 2×10 mL CHCl₃ were added, and solid parts were filtered off. The solvent was evaporated to dryness, and the residue was crystallized from petroleum ether (60–80 °C) to afford the α -phenyl-*N*-methylnitrones.

References: M. A. Bigdeli, M. M. A. Nikje, *Monatsh. Chem.*, **132**, 1547 (2001).

Type of reaction: C–N bond formation**Reaction condition:** solvent-free

Keywords: *o*-phenylenediamine, ketone, Yb(OTf)₃, 2,3-dihydro-1*H*-1,5-benzodiazepine

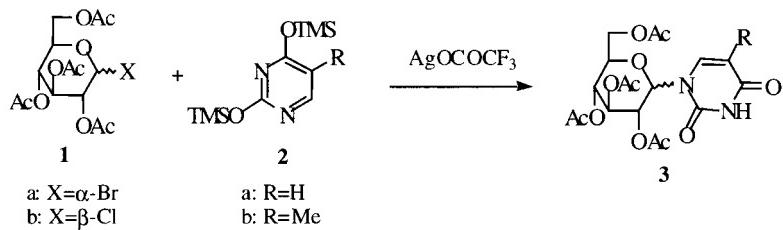
**Experimental procedures:**

A mixture of *o*-phenylenediamine (**1** mmol) and ketone (2.1 mmol) was well stirred with $\text{Yb}(\text{OTf})_3$ (0.05 mmol) at room temperature for 4 h. CH_2Cl_2 (2 mL) was added to crystallized $\text{Yb}(\text{OTf})_3$; the catalyst was removed under reduced pressure and the residue was purified by SiO_2 gel column chromatography using $\text{CH}_2\text{Cl}_2\text{-MeOH}$ (95:5) as eluent.

References: M. Curini, F. Epifano, M.C. Marcotullio, O. Rosati, *Tetrahedron Lett.*, **42**, 3193 (2001).

Type of reaction: C–N bond formation**Reaction condition:** solid-state

Keywords: glucopyranosyl bromide, silylated uracil, silver trifluoroacetate, *N*-glycosylation, *N*-glucosid

**Experimental procedures:**

A mixture of tetra-*O*-acetyl- α -D-glucopyranosyl bromide (0.82 g, 2 mmol) and silver trifluoroacetate (1 g, 4.5 mmol) was ground with mortar and pestle at room

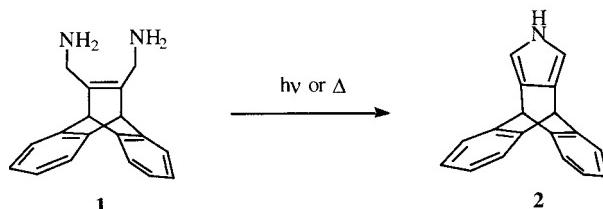
temperature for 5 min under a N₂ atmosphere in a glove box. Then the silylated uracil (0.77 g, 3 mmol) was added to the mixture, which was further ground in a ball mill for 2 days. After quenching the reaction by the addition of water, CHCl₃ was added and the mixture was filtered. Extraction with CHCl₃ and evaporation of the solvent gave a single crude product which was recrystallized from ether-hexane (3:1) to afford 0.43 g (42%) of crystalline product. Mp 147–148 °C.

References: J. Im, J. Kim, S. Kim, B. Hahn, *Tetrahedron Lett.*, **38**, 451 (1997).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: 11,12-bis(aminomethyl)-9,10-dihydro-9,10-ethenoanthracene, pyrrole



Experimental procedures:

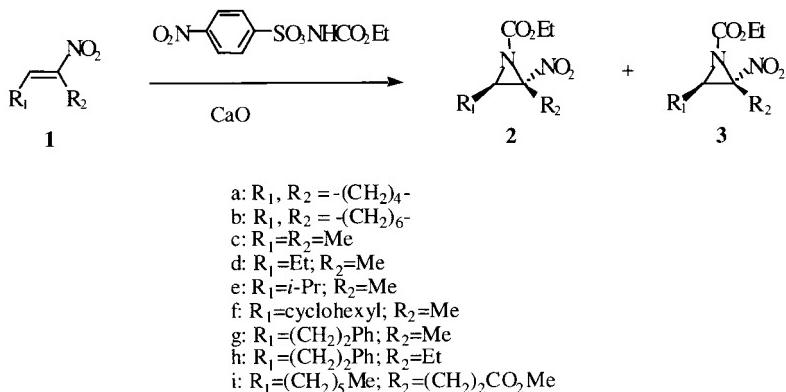
In a quartz flask, 96 mg (0.37 mmol) of **1** were dissolved in tetrahydrofuran and slowly evaporated in *vacuo*, so that a thin layer of solid remained on the wall. The flask was flushed with argon and the sample was irradiated under argon at room temperature for 16 h. Twofold column chromatography gave 11 mg (0.05 mmol, 50%) of **2** as a pale yellow oil that solidified after several days, mp 182 °C.

References: J.R. Scheffer, H. Ihmels, *Liebigs Ann.*, 1925 (1997).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: α -nitroalkene, aziridination, 1-(ethoxycarbonyl)-2-nitroaziridine

**Experimental procedures:**

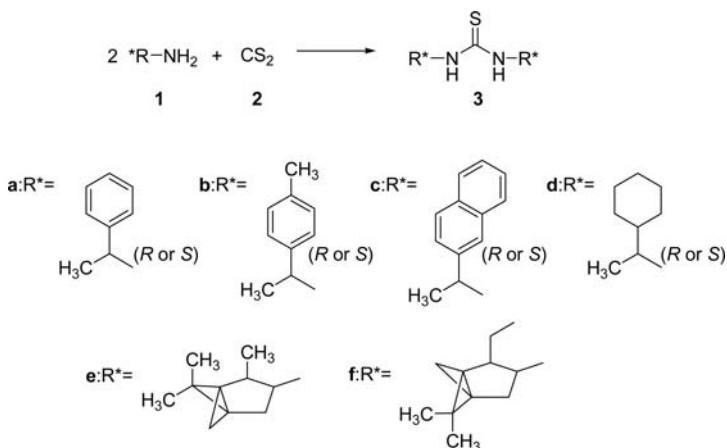
Equimolar amounts of nitroalkene, CaO and ethyl[(4-nitrobenzenesulfonyl)oxy]carbamate were ground in a mortar. After 20 min petroleum ether was added to precipitate the salt. After filtration, the crude mixture was concentrated in vacuo and the 1-(ethoxycarbonyl)-2-nitroaziridines were purified by flash chromatography on silica gel (hexane-ethyl acetate, 8:2).

References: S. Fioravanti, L. Pellaçani, S. Stabile, P.A. Tardella, *Tetrahedron*, **54**, 6169 (1998).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: *N,N*-disubstituted thiourea, carbon disulfide



Experimental procedures:

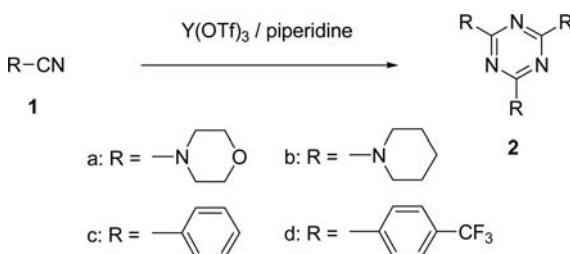
The amine and CS₂ were mixed at room temperature. The obtained precipitate was recrystallized from EtOH affording the corresponding thioureas **3a–f**.

References: J. Vázquez, S. Bernès, Y. Reyes, M. Moya, P. Sharma, C. Alvarez, R. Gutiérrez, *Synthesis*, 1955 (2004).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: 1,3,5-triazine, cyclotrimerization, yttrium trifluoromethanesulfonate

**Experimental procedures:**

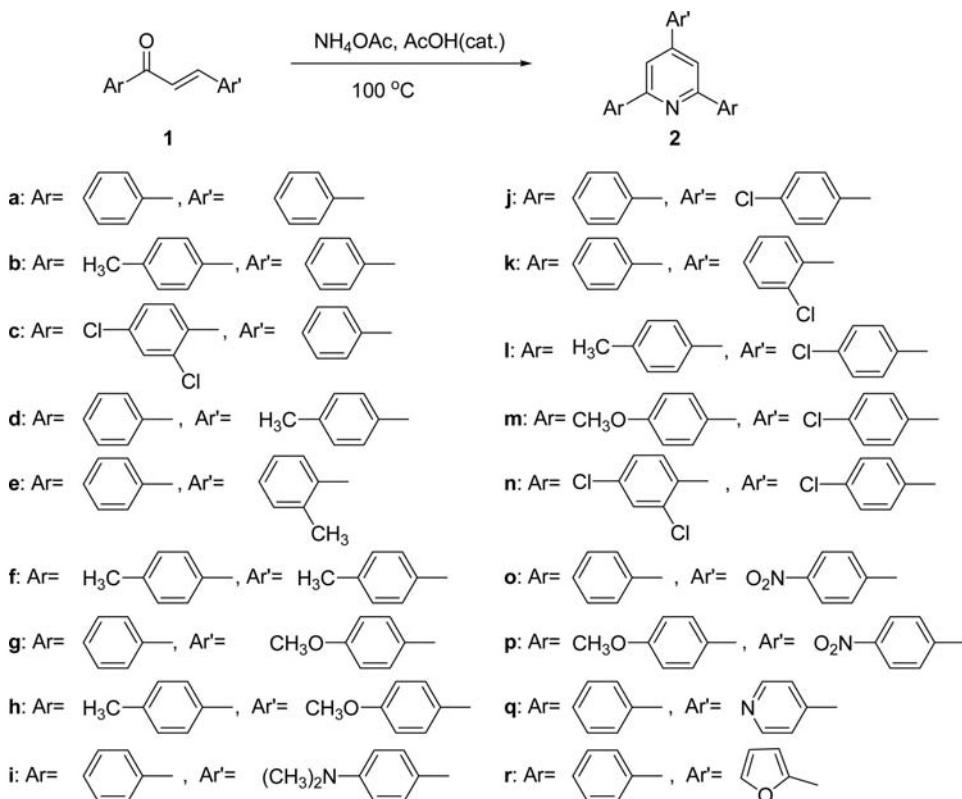
A mixture of yttrium trifluoromethanesulfonate (0.1 mmol, 0.08 g), the appropriate nitrile (10 mmol) and anhydrous piperidine (10 mmol, 1 mL) was heated under argon in a screw-cap sealed reaction vessel in an aluminum block at 200 °C for 24 h.

References: A. Díaz-Ortiz, A. de la Hoz, A. Moreno, A. Sánchez-Migallón, G. Valiente, *Green Chem.*, **4**, 339 (2002).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: Krohnke pyridine, 2,4,6-triarylpyridine, ammonium acetate



Experimental procedures:

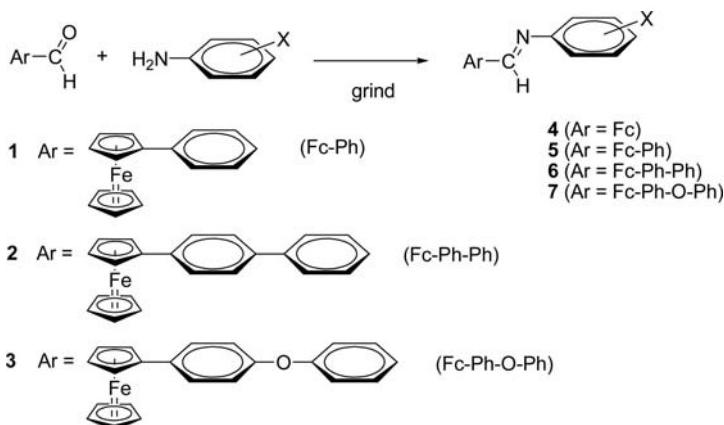
A mixture of 1,3-diphenyl-2-propen-1-one, **1a** (0.42 g, 2 mmol) and ammonium acetate (0.16 g, 2.2 mmol) in the presence of a catalytic amount of acetic acid was stirred at 100 °C for 4 h (progress of the reaction followed by TLC monitoring). The reaction mixture was then cooled to room temperature and the crude solid obtained was recrystallized from absolute ethanol. The product **2a** was obtained in 97% yield as colorless crystals, mp 134–135 °C.

References: M. Adib, H. Tahermansouri, S.A. Koloogani, B. Mohammadi, H.R. Bijanzadeh, *Tetrahedron Lett.*, **47**, 5957 (2006).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: ferrocenylaldehyde, ferrocenylimine



Experimental procedures:

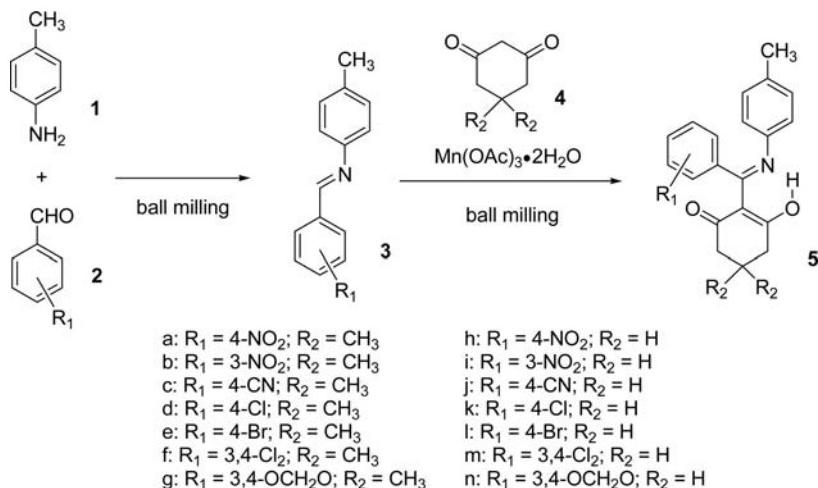
The ferrocenylaldehyde and aniline (equimolar quantities) were added to a pyrex tube fitted with a ground glass joint. The two compounds were ground together using a glass rod at room temperature. In some cases, a gum formed and in others the mixture turned into a melt. The pyrex tube was sealed and then placed on a shaker for approximately 30 min at room temperature. In cases where the starting materials were less reactive, the pyrex tube was immersed in a constant temperature water bath at 50 °C. The samples were then placed under a high vacuum overnight. Initial characterization of the ferrocenylimine was carried out by IR spectroscopy (KBr disk). This indicated replacement of the carbonyl absorption by that of the imine functional group. The ferrocenylimines were finally characterized by ^1H , ^{13}C , mass spectroscopy and microanalysis.

References: C. Imrie, V.O. Nyamori, T.I.A. Gerber, *J. Organometallic Chem.*, **689**, 1617 (2004).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: radical reaction, 1,3-cyclohexanedione, manganese (III) acetate



Experimental procedures:

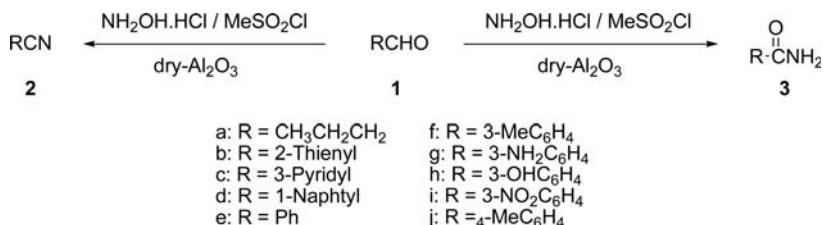
A mixture of aldehyde (0.2 mmol) and 4-methylaniline (0.2 mmol) was introduced, together with a stainless steel ball of 7.0 mm diameter, into a stainless steel jar (5 mL). The same mixture was introduced into another parallel jar. The two reaction vessels were closed and fixed on the vibration arms of a ball-milling apparatus (Retsch MM 200 mixer mill, Retsch GmbH, Haan, Germany), and were milled vigorously at a rate of 1800 rpm at room temperature for 1 h. To the *in situ* generated imines in the two jars were added 0.2 mmol of 1,3-cyclohexanedione and 0.4 mmol of Mn(OAc)₃·2H₂O, respectively. The reaction vessels were then vibrated for a further 3 h. The resulting mixtures were kept overnight and extracted with ethyl acetate and the desired product was separated by flash column chromatography over silica gel.

References: Z. Zhang, G. Wang, C. Miao, Y. Dong, Y. Shen, *Chem. Commun.*, 1832 (2004).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: nitrile, alumina, amide

**Experimental procedures:**

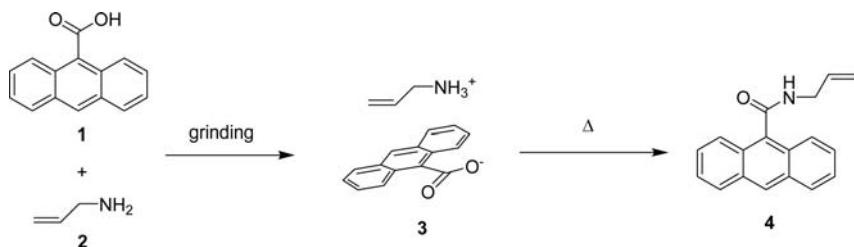
Aldehyde (1 mmol), NH₂OH·HCl (0.3 g, 0.4 mmol), MeSO₂Cl (0.075 ml, 1 mmol) and dry alumina (0.5 g, 4.9 mmol, Fluka type 405 acidic, dried in an oven for 5 h) were thoroughly mixed with a mechanical stirrer. The resulting fine powder was transferred to a round-bottom flask (5 mL) and heated in an oil bath at 100 °C for an appropriate time. Then diethyl ether (10 mL) was added to the reaction mixture and alumina was removed by filtration. The filtrate was extracted with water (2 · 10 mL), dried over Na₂SO₄ and the solvent evaporated *in vacuo* to give the crude product. If solid this was purified by recrystallization from EtOH and if liquid then by distillation.

References: H. Sharghi, M. H. Sarvari, *Tetrahedron*, **58**, 10323 (2002).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: anthracene-9-carboxylic acid, allylamine

**Experimental procedures:**

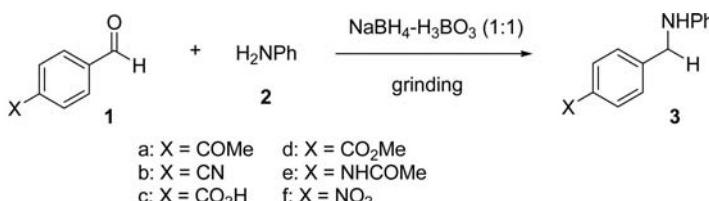
Powdered crystals of 3 were sealed in a stainless still container and heated to 250 °C. The reaction products were separated by chromatography and characterized by comparison with known compounds described in the literature.

References: B. Szczęsna, Z. Urbanczyk-Lipkowska, *CrystEngComm.*, **5**, 385 (2003).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: reductive amination, imine, sodium borohydride



Experimental procedures:

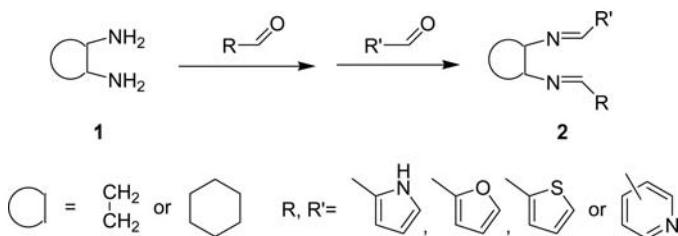
An aldehyde or ketone (5 mmol) was ground with an amine (5 mmol) for 10–15 min using an agate mortar and pestle at room temperature (ca. 25 °C) under solvent-free conditions. To the resulting mixture was added sodium borohydride (5 mmol) and one of boric acid, *p*-toluenesulfonic acid monohydrate or benzoic acid (5 mmol) and then the mixtures were ground under identical conditions until TLC showed complete disappearance of the starting aldehyde. The reaction mixture was quenched with saturated aqueous solution of NaHCO₃ (10 mL) and extracted with CH₂Cl₂ or ether (3 × 10 mL). The combined extract was dried over anhydrous Na₂SO₄, filtered and concentrated. The crude products obtained were further purified by flash column chromatography on silica-gel (230–400 mesh) using a suitable solvent as eluent.

References: B. T. Cho, S. K. Kang, *Tetrahedron*, **61**, 5725 (2005).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: bis-imine, aliphatic diamine



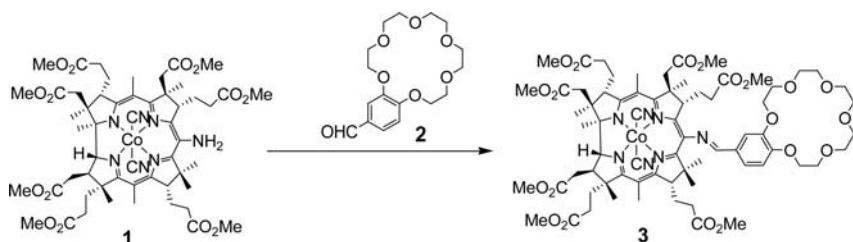
Experimental procedures:

The aldehyde was added to the amine and the mixture agitated (ca. 1 min), affording an oil (ranging from cream to dark brown in color). On further grinding (ca. 5 min) the solid bis-imine product was formed. If required, analytically pure product could be obtained by recrystallization.

References: T.R. van den Ancker, G.W.V. Cave, C.L. Raston, *Green Chem.*, **8**, 50 (2006).

Type of reaction: C–N bond formation**Reaction condition:** solid-state

Keywords: vitamin B₁₂, benzo-18-crown-6

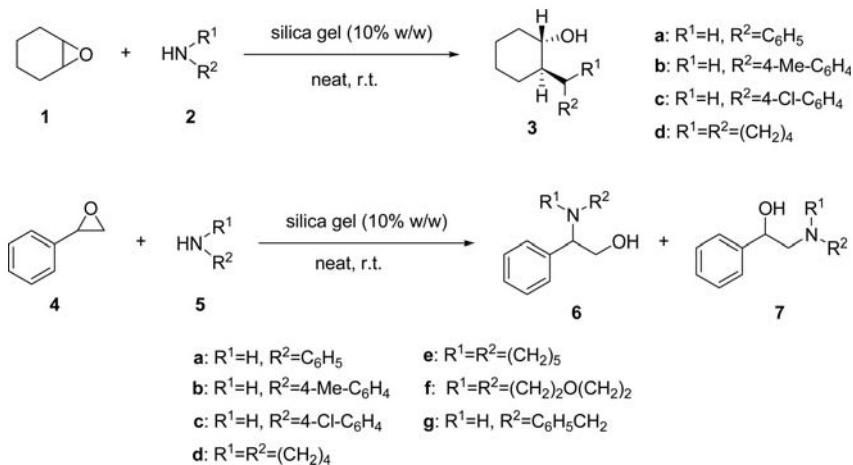
**Experimental procedures:**

9.08×10^{-6} mol of **1** and one equivalent mol of **2** were dissolved in dichloromethane and the solvent was evaporated to dryness. The homogeneous mixture of **1** and **2** was allowed to stand for 156 h at room temperature under a nitrogen atmosphere to form the condensation product **3** in 56% isolated yield.

References: H. Shimakoshi, T. Inaoka, Y. Hisaeda, *Tetrahedron Lett.*, **44**, 6421 (2003).

Type of reaction: C–N bond formation**Reaction condition:** solvent-free

Keywords: silica gel, 2-amino alcohol, epoxide



Experimental procedures:

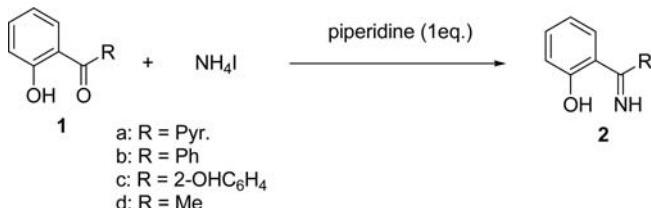
Silica gel (60–120 mesh, 25 mg, 10%w/w) was added to a magnetically stirred mixture of **1** (0.25 mL, 2.5 mmol) and **2a** (0.225 mL, 2.5 mmol) at room temperature under nitrogen. After completion of the reaction (3 h, GCMS), the reaction mixture was diluted with Et₂O (15 mL) followed by addition of a few drops of water (to settle down the catalyst). The catalyst was separated by decantation of the supernatant ethereal solution, washed with Et₂O (10 mL) and the combined ethereal solutions were dried (Na₂SO₄) and concentrated under vacuum to afford trans-2-(phenylamino)cyclohexanol **3a** (0.428 g, 90%).

References: A. K. Chakraborti, S. Rudrawar, A. Kondaskar, *Org. Biomol. Chem.*, **2**, 1277 (2004).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: 2-(2-hydroxybenzoyl)pyridine, ammonium iodide



Experimental procedures:

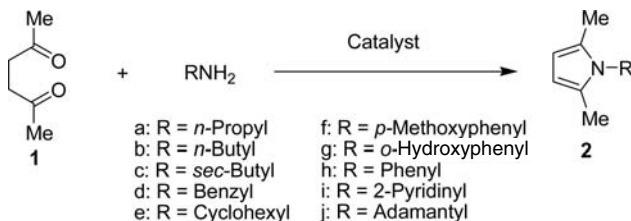
Piperidine (27 mL, 0.27 mmol) was added to a mixture of 2-(2-hydroxybenzoyl)-pyridine **1a** (50 mg, 0.25 mmol) and ammonium iodide (40 mg, 0.27 mmol). The resulting mixture was heated to 35 °C for 40 h. For an analytically pure sample, the product mixture was isolated by chromatography on silica gel using ethyl acetate:hexane (1:4) to remove any unreacted ketone, followed by ethyl acetate to obtain the pure imine **2a** as a yellow solid.

References: Y. Bergman, P. Perlmutter, N. Thienthong, *Green Chem.*, **6**, 539 (2004).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: pyrrole, zirconium phosphate, heterogeneous catalyst



Catalyst = α -Zr(KPO₄)₂, α -Zr(CH₃PO₃)_{1.2}(O₃PC₆H₄SO₃H)_{0.8}

Experimental procedures:

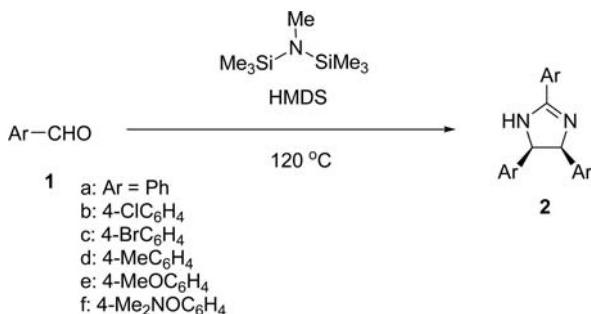
To a mixture of amine (2 mmol) and 2,5-hekanedione (1 mmol), under stirring and at room temperature (or 60 °C), catalyst (12 mol% for α -Zr(KPO₄)₂ or 6 mol% for α -Zr(CH₃PO₃)_{1.2}(O₃PC₆H₄SO₃H)_{0.8}) was added. After an appropriate time the reaction was diluted with dichloromethane, filtered on a Buchner filter and washed with a 5% HCl solution to remove the excess amine. The organic solution was evaporated under vacuum and afforded the pyrrole derivative with good purity.

References: M. Curini, F. Montanari, O. Rosati, E. Lioy, R. Margarita, *Tetrahedron Lett.*, **44**, 3923 (2003).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: imidazoline, hexamethyldisilazane, 2,4,5-triarylimidazoline



Experimental procedures:

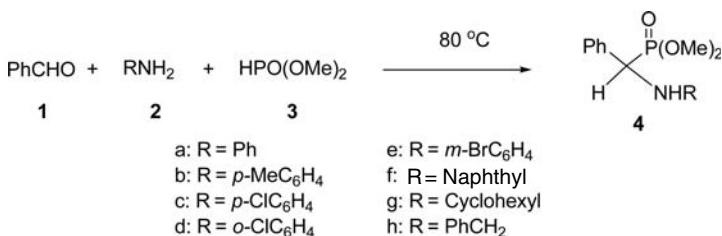
A mixture of benzaldehyde (**1a**; 157 mg, 1.5 mmol) and hexamethyldisilazane HMDS (342 mL, 260 mg, 1.6 mmol) was heated in a sealed tube at 120 °C for 6 h. A yellowish-white precipitate appeared during the heating. After cooling, the volatile compounds were removed under vacuum to leave a residue which was purified by silica gel column chromatography using hexane–EtOAc (9:1) as eluent to give 131 mg (89%) of **2a**; mp 132.0–133.0 °C (toluene–n-hexane).

References: H. Uchida, T. Shimizu, P.Y. Reddy, S. Nakamura, T. Toru, *Synthesis*, 1236 (2003).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: *a*-aminophosphonate, Kabachnik-Fields reaction, dimethyl phosphite



Experimental procedures:

Benzaldehyde (1 mmol), aniline (1 mmol), and dimethyl phosphate (2 mL) were added to a 25-ml three-necked flask. The mixture was stirred at 80 °C for 2 h. The reaction mixture was then diluted with water and extracted with CH₂Cl₂.

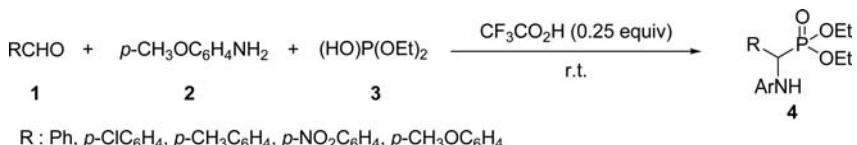
(20 mL). The organic layer was washed with H₂O (3×10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was purified by silica gel flash column chromatography eluted with 2:1 petroleum ether–acetone to give pure *α*-aminophosphonate **4a** in 85% yield.

References: X.-J. Mu, M.-Y. Lei, J.-P. Zou, W. Zhang, *Tetrahedron Lett.*, **47**, 1125 (2006).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: *α*-amino phosphonate



Experimental procedures:

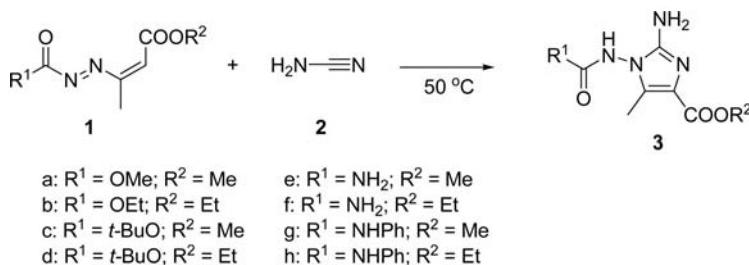
To a mixture of benzaldehyde (940 μL, 9.26 mmol), *p*-anisidine (1.15 g, 9.33 mmol), and diethyl phosphate (1.80 mL, 14.0 mmol) was added trifluoroacetic acid (180 μL, 2.34 mmol) at room temperature. After being stirred for 24 h at room temperature, the mixture was quenched by addition of saturated NaHCO₃ solution. The reaction mixture was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated to dryness. Purification by column chromatography (SiO₂, hexane–ethyl acetate=1:1 v/v) gave *α*-amino phosphonate (3.23 g) in a quantitative yield.

References: T. Akiyama, M. Sanada, K. Fuchibe, *Synlett*, 1463 (2003).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: Michael addition, 1,2-diaza-1,3-butadiene, 1,2-diaminoimidazole



Experimental procedures:

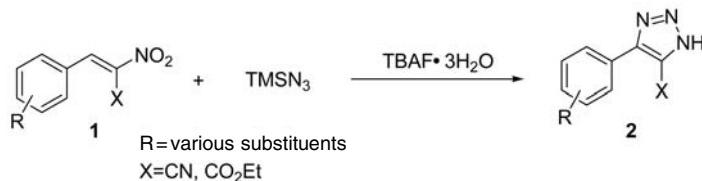
The appropriate 1,2-diaza-1,3-butadienes **1a–h** (0.3 mmol) were reacted with ananamide **2** (0.6 mmol) in solvent-free conditions and heated at 50°C . Immediately the red color of azoalkene disappeared and the crude mixture was purified by chromatography on a preparative silica gel plate with cyclohexane–EtOAc (10:90) affording products **3a–h**.

References: O. A. Attanasi, L. de Crescentini, G. Favi, P. Filippone, F. Mantellini, S. Santusiano, *Synlett*, 549 (2004).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: 4-aryl-1*H*-1,2,3-triazole, [3+2]cycloaddition, 2-aryl-1-nitroethane



Experimental procedures:

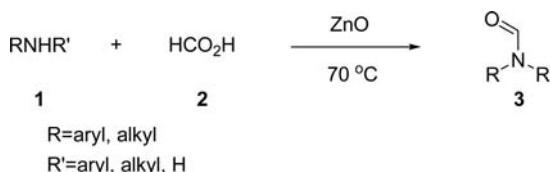
In a screw-capped vial equipped with a magnetic stirrer, $\text{TBAF}\cdot 3\text{H}_2\text{O}$ (0.064 g, 0.2 mmol), (*E*)-1-cyano-2-phenyl-1-nitroethane (**1**: R=H, X=CN) (0.348 g, 2.0 mmol), and TMSN_3 (0.460 g, 4.0 mmol) were consecutively added, and the resulting mixture was left under vigorous stirring at 30°C for 3 h. The crude reaction mixture was charged on a silica gel column chromatography (petroleum ether/ethyl acetate 8/2 (gradient); silica/sample 15:1). Pure 4-phenyl-1*H*-1,2,3-triazole-5-carbonitrile (**2**: R=H, X=CN) was isolated as a white solid in 85% yield (0.289 g). The product was recrystallized from ethyl acetate to give white crystals, mp 185–186 °C.

References: D. Amantini, F. Fringuelli, O. Piermatti, F. Pizzo, E. Zunino, L. Vaccaro, *J. Org. Chem.*, **70**, 6526 (2005).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: *N*-formylation, ZnO, formamide



Experimental procedures:

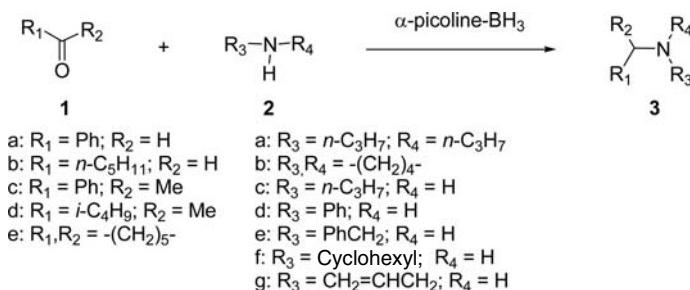
To a mixture of HCO_2H (3 mmol, 0.11 mL) and ZnO (0.5 mmol, 0.04 g) was added an amine (1 mmol), and then the reaction mixture was heated in an oil bath at 70°C and stirred with a magnetic stirrer. The progress of the reaction was monitored by TLC. After the reaction was complete, CH_2Cl_2 or EtOAc was added to the reaction mixture and ZnO was removed by filtration. The organic solvent was then washed with H_2O (2×10 mL) and a saturated solution of NaHCO_3 and dried over anhydrous Na_2SO_4 . After removal of the solvent, the pure product was obtained.

References: M. Hosseini-Sarvari, H. Sharghi, *J. Org. Chem.*, **71**, 6652 (2006).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: reductive amination, aldehyde, *a*-picoline-borane



Experimental procedures:

To acetophenone **1c** (1.00 g, 8.32 mmol), benzylamine **2e** (0.89 g, 8.32 mmol), and AcOH (0.3 ml) was added picoline-BH₃ (0.89 g, 8.32 mmol) over 5 min and the reaction mixture was stirred for 72 h. After the reaction, 19% HCl (10 mL) was added and the aqueous solution was stirred for 0.5 h at room temperature.

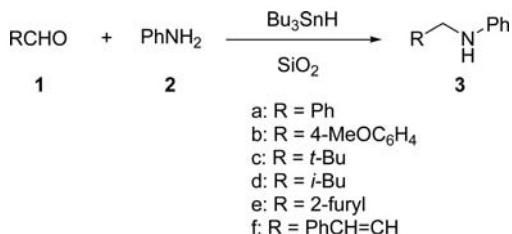
Na_2CO_3 (ca. 2.5 g) and H_2O (10 mL) were added to the solution under cooling to make the solution alkaline. The aqueous layer was extracted with AcOEt ($30 \text{ mL} \times 2$), and the combined organic layer was washed with brine (15 mL), dried over Na_2SO_4 , and concentrated. The crude product was chromatographed on a column of silica gel with $\text{AcOEt}-n\text{-hexane}$ (1:3) to afford *N*-benzyl-1-phenylethylamine (1.53 g, 87%).

References: S. Sato, T. Sakamoto, E. Miyazawa, Y. Kikugawa, *Tetrahedron*, **60**, 7899 (2004).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: tributyltin hydride, silica gel, imine, reduction



Experimental procedures:

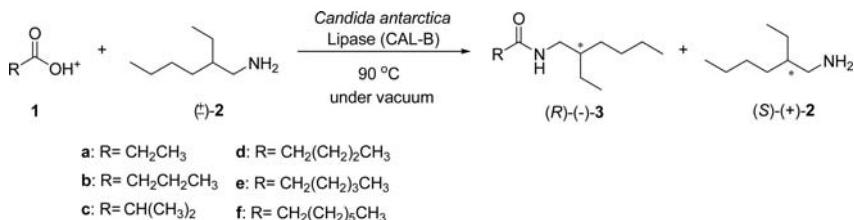
Bu_3SnH (0.291 g, 1.0 mmol) was added at ambient temperature to a mixture of benzaldehyde (0.106 g, 1.0 mmol) and aniline (0.930 g, 1.0 mmol) on dried silica gel (dried by heat gun, 1600 mg). The reaction mixture was stirred at the same temperature for only 1 h, and then the organic materials were extracted with diethyl ether ($30 \text{ mL} \times 3$). After evaporation of the solvent, the residue was purified by thin-layer chromatography on silica gel (hexane: $\text{AcOEt}=5:1$) to afford the corresponding product, benzyl phenyl amine (0.183 g, 100% yield).

References: R. Hiroi, N. Miyoshi, M. Wada, *Chem. Lett.*, **31**, 274 (2002).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: candida antarctica, lipase, amidation



Experimental procedures:

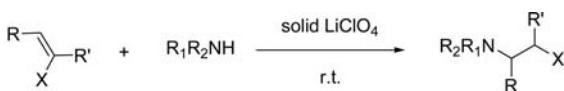
To a mixture of the acid (**1a–f**, 2.5 mmol) and racemic 2-ethylhexyl amine (2, 5.0 mmol), CAL-B (300 mg) was added. The reaction mixture was heated at 90 °C *in vacuo* with stirring and the progress of the reaction was monitored by IR spectroscopy. When the acid was consumed completely, the reaction mixture was diluted with dichloromethane and quenched by filtering off the enzyme. The organic solvent was evaporated *in vacuo* and the residue was subjected to column chromatography using petroleum ether–ethyl acetate as eluent to afford the pure amide and the unreacted amine in optically enriched forms.

References: A.K. Prasad, M. Husain, B.K. Singh, R.K. Gupta, V.K. Manchanda, C.E. Olsen, V.S. Parmar, *Tetrahedron Lett.*, **46**, 4511 (2005).

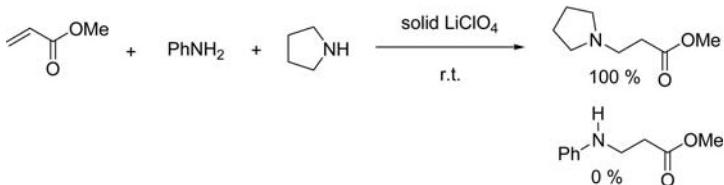
Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: Michael reaction, lithium perchlorate



R = H, Ph; R' = CH₃; X = CN, CONH₂, COOMe, COMe



Experimental procedures:

To a mixture of LiClO₄ (2 mmol) and methyl acrylate (2 mmol) was added pyrrolidine (3 mmol) and the mixture was stirred at room temperature under an argon atmosphere for 1 h. After completion of the reaction, CH₂Cl₂ (10 mL) was added, and LiClO₄ was removed by filtration. The solvent was evaporated and

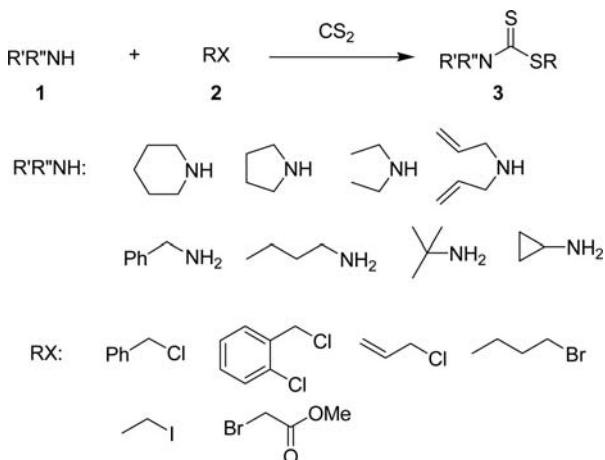
the product was isolated in almost pure form. Further purification was carried out by short column chromatography on silica gel eluting with ethyl acetate–petroleum ether.

References: N. Azizi, M.R. Saidi, *Tetrahedron*, **60**, 383 (2004).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: S-alkyl dithiocarbamate, carbon disulfide



Experimental procedures:

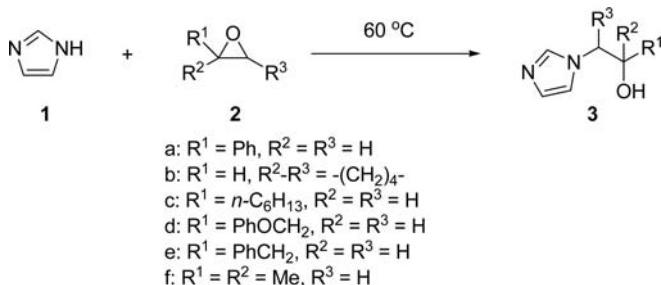
To an ice cold mixture of the organic halide (3 mmol) and carbon disulfide (6 mmol) in a test tube was added amine (6 mmol) and the mixture was stirred at 0 °C for 30 min, then warmed to room temperature where stirring was continued until the reaction was complete (reaction mixture solidified or monitored by TLC). The reaction was quenched by addition of water and was extracted with EtOAc, dried over anhydrous Na₂SO₄, and evaporated to give NMR pure product. Further purification in some cases could be achieved by silica gel column chromatography eluted with petroleum ether and ethyl acetate or recrystallization to afford the pure dithiocarbamate.

References: N. Azizi, F. Aryanab, M.R. Saidi, *Org. Lett.*, **8**, 5275 (2006).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: imidazole, epoxide, 1-(β-hydroxyalkyl)imidazole



Experimental procedures:

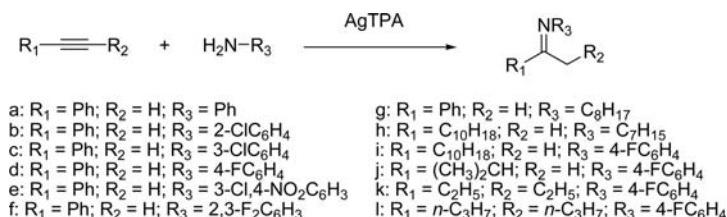
A mixture of imidazole (20 mmol, 1.38 g) and epoxide (20 mmol) was placed in a round-bottom flask and stirred at $60\text{ }^\circ\text{C}$ (except for the epoxide **2f** where reaction was carried out at $45\text{ }^\circ\text{C}$) for 12 h. The resulting mixture was purified by recrystallization (normally using acetone/hexane or dichloromethane/hexane) and/or by column chromatography (silica gel, mixtures of ethyl acetate and methanol from 20:1 to 30:1) to yield the corresponding imidazolyl alcohols **3**.

References: R. Torregrosa, I.M. Pastor, M. Yus, *Tetrahedron*, **63**, 469 (2007).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: hydroamination, alkyne, silver-exchanged tungstophosphoric acid



Experimental procedures:

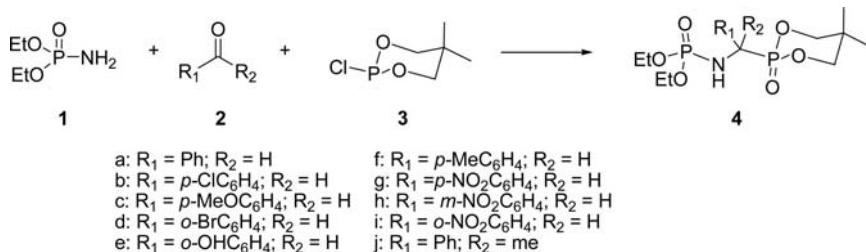
Under a nitrogen atmosphere, a mixture of phenyl acetylene (1 mmol), 4-fluoroaniline (1.2 mmol) and AgTPA (silver metal exchanged tungstophosphoric acid, 50 mg) was stirred at $70\text{ }^\circ\text{C}$ for 2 h. The progress of the reaction was monitored by TLC and, on completion, the mixture was cooled and hexane (10 mL) was added to precipitate the corresponding product. The product was recrystallized from hexane-dichloromethane to give 4-fluoro-N-(methylbenzylidene)aniline (99% yield).

References: N. Lingaiah, N.S. Babu, K.M. Reddy, P.S.S. Sai, I. Suryanarayana, *Chem. Commun.*, 278 (2007).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: *N*-phosphoramino, α -aminophosphonate, Mannich-type reaction



Experimental procedures:

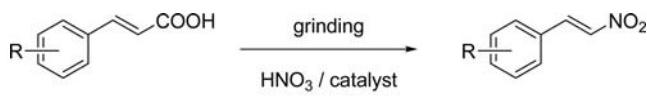
Ketones or aldehydes (1 mmol) were added to a stirred mixture of diethyl phosphoramide **1** (1 mmol) and 2-chloro5,5-dimethyl-1,3,2-dioxaphosphane **3** (1 mmol) at 50–60 °C. After stirring for the corresponding amount of time, the mixture went slimy and the reactions were stopped. The crude products were purified by flash chromatography on silica gel (started with ethyl acetate–petroleum ether 4:1, and then pure ethyl acetate as eluent). Their structures were characterized by ¹H NMR, ³¹P NMR, ¹³C NMR and elemental analysis.

References: J. Zhanwei, Z. Cui, F. Wang, Y. Wang, Z. Miao, R. Chen, *Green Chem.*, 1341 (2007).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: Hunsdiecker reaction, β -nitro styrene



R : H, 4-Cl, 4-MeO, 4-Me, 4-NO₂, 4-OH

catalyst: Mg(NO₃)₂, Sr(NO₃)₂, Al(NO₃)₃, Ca(NO₃)₂ etc

Experimental procedures:

Cinnamic acid (0.01 mol), metal nitrate (0.015 mol) and a few drops of nitric acid were taken in a mortar and ground for about 1–2 h. After completion, as ascertained by TLC, the reaction mixture was treated with 2% sodium carbonate solution, followed by the addition of dichloromethane or dichloroethane. The organic layer was separated, dried over Na₂SO₄ and evaporated under vacuum,

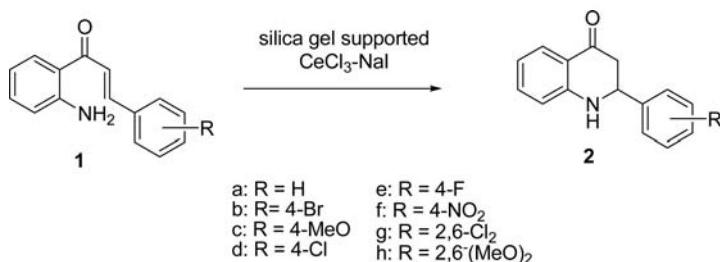
then purified by column chromatography using ethyl acetate–hexane (3:7) as eluent to afford the pure product.

References: S. Ramgopal, K. Ramesh, A. Chakradhar, N.M. Reddy, K.C. Rajanna, *Tetrahedron Lett.*, **48**, 4043 (2007).

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: 2'*a*-aminochalcone, 2-aryl-2,3-dihydroquinolin-4(1*H*)-one



Experimental procedures:

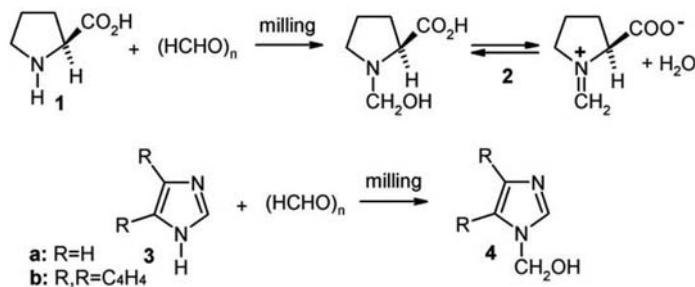
Aminochalcone (1.0 mmol) was dissolved in CH₂Cl₂ (1–1.5 mL) and alumina supported CeCl₃·7H₂O–NaI (300–400 mg) or silica gel supported catalyst (300–400 mg) was added. The solvent was evaporated by heating and the resulting powdered reaction mixture was further heated for an additional 2–2.5 h at 70 °C. After completion of the reaction (by TLC monitoring), the mixture was cooled to room temperature and the product was recovered by washing with diethyl ether and evaporation of the solvent. Alternatively the reaction mixture was directly applied to a silica gel column and eluted with hexane–CH₂Cl₂ (1:9) to afford the pure products.

References: N. Ahmed, J.E. van Lier, *Tetrahedron Lett.*, **48**, 13 (2007).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: proline, paraformaldehyde, imidazole, benzimidazole, large scale, N/O acetals, solid-solid reaction, ball milling, quantitative



Experimental procedures:

Mixtures of (*L*)-proline **1** (173 g, 1.50 mol) and 98% paraformaldehyde (46.0 g, 1.50 mol) were milled in a 2-L hard metal horizontal rotary ball mill (Simo-layer®) with 2 kg steel balls (100Cr6; 5 mm diameter) at 1000 min⁻¹ and with external water cooling (15–19 °C gradient) for 30 min. Spectroscopic techniques confirmed 100% conversion and 100% yield of **2** that occurs as iminium carboxylate in polar solvents. The product **2** was milled out for 10 min at 600 min⁻¹ leaving some hold-up, but a quantitative recovery was obtained from the second batch and so on. For quantitative recovery of the last batch an internal air cycle for collection through a cyclone should be used [1].

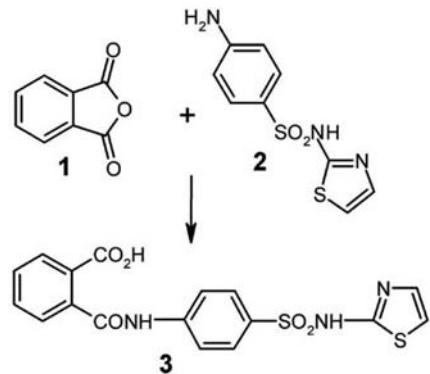
Similarly to the procedure for **2**, 200 g quantities of stoichiometric mixtures of imidazole **3a** or benzimidazole **3b** with paraformaldehyde were milled at 0–5 °C or 15–20 °C, respectively, to provide quantitative yields of **4a**, mp 45 °C or **4b**, mp 140 °C [2].

- References:** 1. G. Kaupp, *CrystEngComm* **8**, 794 (2006).
2. G. Kaupp, *Top. Curr. Chem.* **254**, 95 (2005).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: large scale, phthalic anhydride, aniline sulfonamide, phthalazole, solid-solid reaction, solid-solid reaction, ball mill



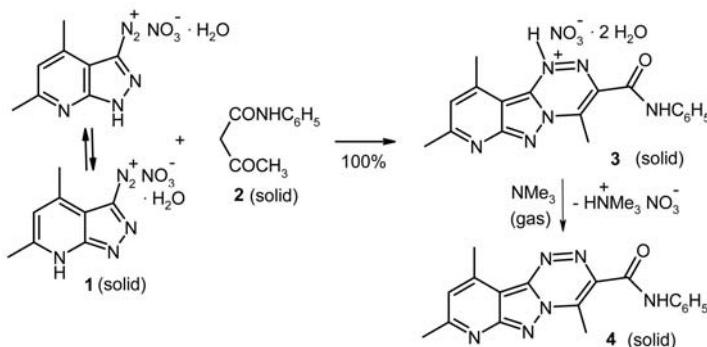
Experimental procedure:

200 g quantities of a stoichiometric 1:1-mixture of loosely premixed crystals of **1** and **2**, both at >99% purity, were fed to a hardmetal 2-L horizontal rotary ball mill (Simoloyer®) with 2 kg steel balls (100Cr6; 5 mm diameter) at 1000 min⁻¹ with water cooling at 15–20°C for 1 h. The quantitatively formed antibacterial phthalazole **3**, mp 270°C, was free from bisamide side products, which occur upon reaction in solution or in the melt. The product **3** was milled out for 10 min at 600 min⁻¹ leaving some hold-up, but a quantitative recovery was obtained from the second batch and so on. For quantitative recovery of the last batch an internal air cycle for deposition through a cyclone should be used. Semicontinuous production is possible.

References: G. Kaupp, *CrysEngComm* **8**, 794 (2006).

Type of reaction: C–N bond formation**Reaction condition:** solid-state

Keywords: quantitative, solid diazonium salt, pyrazolopyridine, azo coupling, solid-solid reaction, solid-solid reaction, solid-gas reaction, cascade reaction

**Experimental procedure:**

Caution: Solid diazonium salts explode upon shock and upon grinding at sharp edges; do not ball mill; grind cautiously!

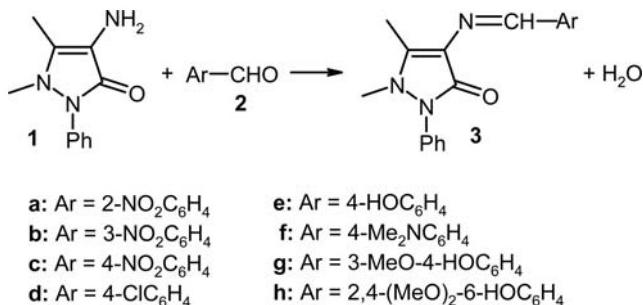
The acetoacetanilide **2** (2.00 mmol) was ground in an agate mortar. The solid diazonium nitrate hydrate (2.00 mmol) was added and co-ground in five portions for 10 min each to obtain **3** that was transferred to a 100-mL flask that was then evacuated. The salt was exposed to trimethylamine gas (0.5 bar) overnight at room temperature. After recovery of excess gas from a trap at 77 K the trimethylammonium nitrate was washed away with water (20 mL) and the pure residual **4** (664 mg, 100%, mp 273°C) dried *in vacuo*.

References: G. Kaupp, M. A. Metwally, F.A. Amer, E. Abdel-latif, *Eur. J. Org. Chem.* **2003**, 1545.

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: aminoantipyrine, benzaldehydes, azomethines, quantitative, solid-solid reaction, ball mill



Experimental procedure:

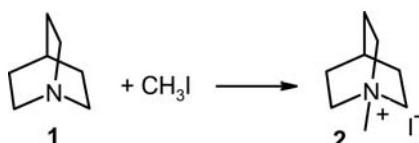
A mixture of 4-aminoantipyrine **1** (0.406 g, 2.00 mmol) and the solid aldehyde **2** (2.00 mmol) was ball-milled at room temperature for 1 h. The solid powder was dried at 80 °C *in vacuo* to give pure **3** with 100% yield and did not require purifying work-up.

References: E. Abdel-Latif, G. Kaupp, M. A. Metwally, *J. Chem. Res.* **2005**, 187.

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: gas-solid reaction, quinuclidine, methyl iodide, quaternary salt, quantitative



Experimental procedure:

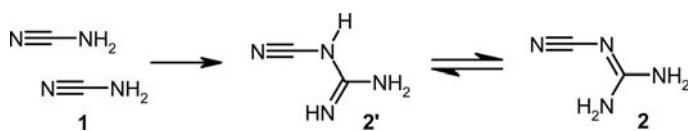
A 50-mL flask containing iodomethane (310 mg, 2.18 mmol) was connected at a vacuum line to a 50-mL flask containing quinuclidine **1** (242.5 mg, 2.18 mmol) at 40 °C in an ultrasound cleaning bath, in order to facilitate the difficult separation of the crystals of **2** from those of **1**. The gas-tight flasks were left for 12 h to produce the quaternary salt **2** (552 mg, 100%) in pure form.

References: G. Kaupp, *Top. Curr. Chem.* **254**, 95 (2005).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: melt reaction, intracrystalline reaction, cyanamide, cyanoguanidine



Experimental procedures:

Cyanamide **1** (5 g) was melted and heated to 120 °C for 10 min to obtain the solid cyanoguanidine **2**, mp 205 °C in quantitative yield.

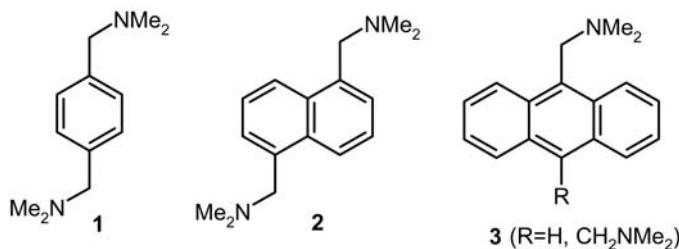
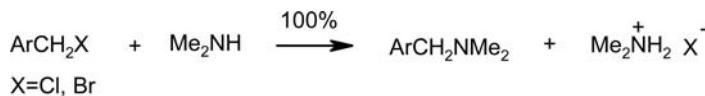
A 1 kg supply of dry crystalline **1** was stored at ambient temperature for more than one year and was thereafter completely transformed to crystalline **2**.

References: G. Kaupp, *Top. Curr. Chem.* **254**, 95 (2005).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: gas-solid reaction, benzyl halides, benzyl amines



Experimental procedure:

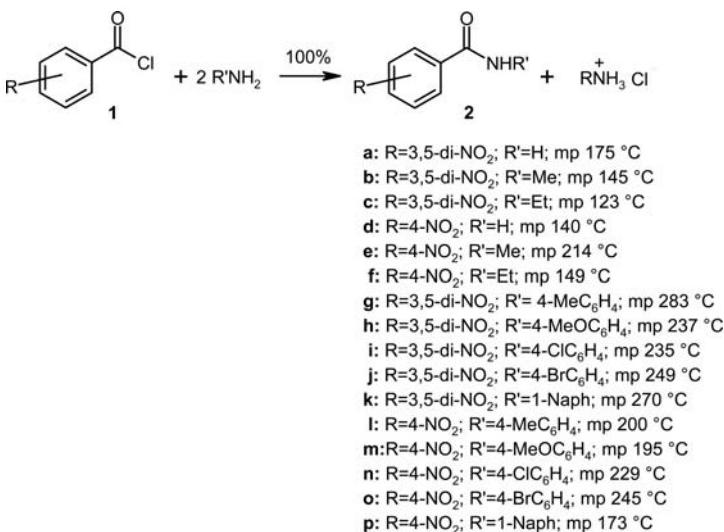
The solid benzylic bromide (for **1** and **2**) or chloride (for **3**) (2.00 mmol) in an evacuated 50-mL flask was exposed to dimethylamine gas from a lecture bottle (1 bar) at room temperature overnight. The quantitatively obtained *N,N*-dimethylbenzylamines were obtained in pure form after condensation of the excess gas to a trap at 77 K for recovery, washing with water, and drying in a vacuum.

References: G. Kaupp, *Top. Curr. Chem.* **254**, 95 (2005).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: gas-solid reaction, solid-solid reaction, aroylchlorides, arylamides



Experimental procedures:

The solid arylchloride **1** (1.00 mmol) in an evacuated 100-mL flask was exposed to the gaseous amine (0.5 bar) and left overnight at room temperature to give the arylamides **2a–f** quantitatively. The excess gas was collected in a trap at 77 K for recovery and **2a–f** were obtained in pure form after washing with water to remove the salt by-product and drying in a good vacuum.

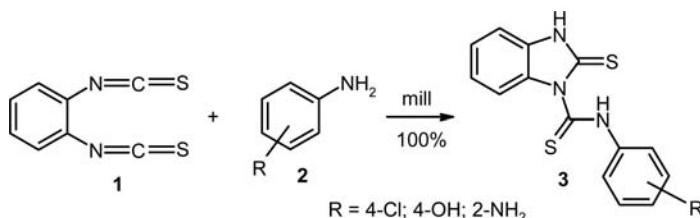
The solid arylchloride **1** (1.00 mmol) and the solid arylamine (2.00 mmol) were ball-milled at 0 °C for 1 h, to give the arylamides **2g–p** quantitatively. These were dried after removal of the ammonium salts by washing with water.

References: G. Kaupp, *Top. Curr. Chem.* **254**, 95 (2005).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: solid-solid reaction, cascade reaction, anilines, 1,2-diisothiocyanato benzene, thioureas, quantitative

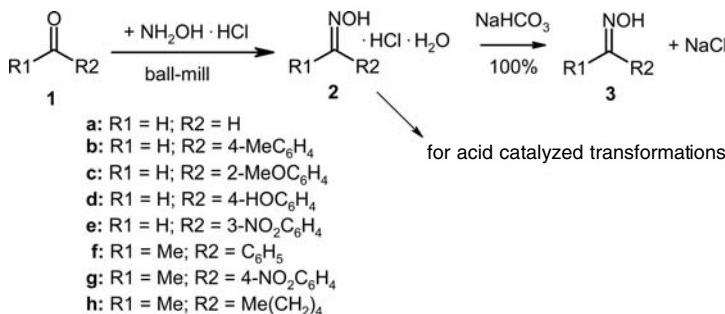
**Experimental procedure:**

The aniline **2** (2.00 mmol) and 1,2-diisothiocyanato benzene **1** (2.00 mmol) were ball-milled for 1 h at 25 °C to give a quantitative yield of pure **3**.

References: G. Kaupp, J. Schmeyers, J. Boy, *Tetrahedron* **56**, 6899 (2000).

Type of reaction: C–N bond formation**Reaction condition:** solvent-free

Keywords: kneading ball milling, quantitative, condensation reaction, aldehydes, hydroxylamine, hydroxylamine, oximes

**Experimental procedure:**

Hydroxylamine hydrochloride (5.00 mmol) and the aldehyde or ketone **1** (5.00 mmol) were kneading ball-milled in a double-walled 10-mL stainless steel vessel with two balls of 12 mm diameter at 20–25 Hz for 10 min at 45–50 °C (**a–e**) or for 30 min at 65–70 °C (**f–h**). A quantitative yield of the oxime hydrochloride hydrate **2** was obtained. The salt **2** already carries the catalyst for most of the various synthetic uses of the oximes. Washing with aqueous NaHCO₃, if required, can liberate the free oximes **3**.

Alternatively, ball milling of mixtures of **1** (1.00 mmol) and hydroxylamine hydrochloride (1.00 mmol) and NaHCO₃ (1.00 mmol) for the same times and temperatures gave **3** (100%) mixed with NaCl. The CO₂ escaped through a moderately tightened Teflon gasket and the water of reaction was evaporated in a vacuum.

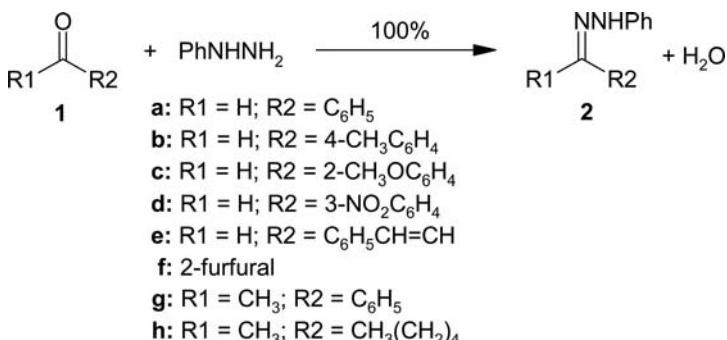
Similarly, 10 mmol runs of **1b,e** with hydroxylamine hydrochloride to give **2b,e** were successfully performed in the same 10-mL vessel.

References: J. Mokhtari, M.R. Naimi-Jamal, H. Hamzeali, M.G. Dekamin, G. Kaupp, *ChemSusChem* (2008), submitted; there further examples.

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: melt reaction, quantitative, condensation reaction, aldehydes, ketones, phenylhydrazones, phenylhydrazone



Experimental procedure:

Caution: Phenylhydrazine is a poisonous carcinogenic agent that must be handled with extreme care and should be completely transformed for safe handling.

Phenylhydrazine (about 5 mmol precisely weighed) and the stoichiometric amount of the aldehyde **1a–f** were rapidly mixed in a beaker at room temperature. The pure phenylhydrazone **2a–f** quantitatively crystallized from the liquid with considerable heat production. The water of reaction was removed by evaporation in a vacuum for 1 h.

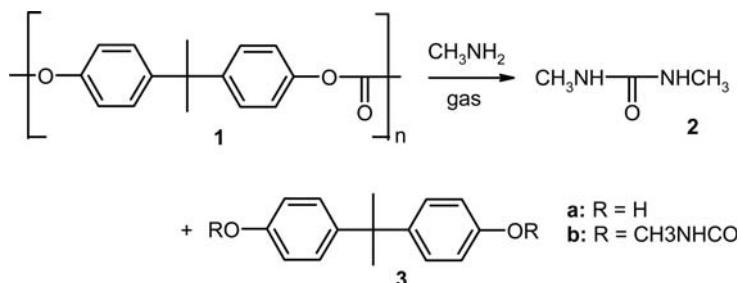
Similarly, the liquid stoichiometric mixture of phenylhydrazine and the ketone **1g–h** was heated to 65–70 °C for 20 min. A quantitative yield of the crystalline phenylhydrazone **2g–h** was obtained after drying in a vacuum.

References: J. Mokhtari, M.R. Naimi-Jamal, H. Hamzeali, M.G. Dekamin, G. Kaupp, *ChemSusChem* (2008), submitted; includes further examples.

Type of reaction: C–N bond formation

Reaction condition: solvent-free

Keywords: polycarbonate, methylamine, *N,N'*-dimethylurea, bisphenol A, aminolysis, aminolysis



Experimental procedure:

Polycarbonate Makrolon® pieces **1** (5 g) were placed in a short column with glass frit and ground joints fitted to a flask with evaporation facility and with a gas supply at the top. After evacuation and closing with a stopcock a constant pressure of 0.9–1 bar of methylamine gas was applied and maintained for 1–3 h, depending on the size of the pieces of **1**, until all of it had liquefied and dropped into the flask. The residual gas was recovered from a trap at 77 K. The liquid contained *N,N'*-dimethylurea **2** and bisphenol A **3a** as the major products and also some urethane and bisurethane **3b**, ready for separation work-up.

References: G. Kaupp, J. Schmeyers, J. Boy, *Tetrahedron* **56**, 6899 (2000).

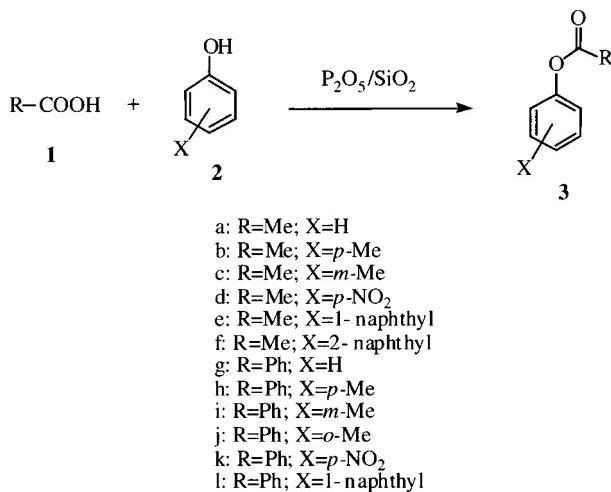
5 Carbon–Oxygen Bond Formation

5.1 Solvent-Free C–O Bond Formation

Type of reaction: C–O bond formation

Reaction condition: solid-state

Keywords: phenol, carboxylic acid, P₂O₅/SiO₂, ester



Experimental procedures:

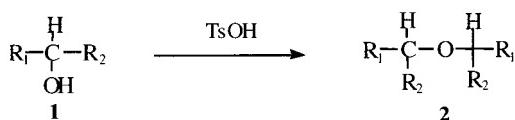
A mixture of 1.42 g (0.01 mol) phosphorus pentoxide and 2.5 g of chromatography grade silica gel was placed in a flask and stirred for 30 min. A mixture of equimolar amounts (5 mmol) of the carboxylic acid and phenol was added. Usually an immediate color change was observed. After stirring for 6 h at the temperature indicated in the Table, methylene chloride (50 mL) was added. The mixture was stirred for 1 min and then filtered. The spent reagent was washed twice with methylene chloride (10 mL). The combined organics were washed with aqueous NaOH solution, water and dried over sodium sulfate, and the solvent was removed under reduced pressure.

References: H. Eshghi, M. Rafei, M. H. Karimi, *Synth. Commun.*, **31**, 771 (2001).

Type of reaction: C–O bond formation

Reaction condition: solid-state

Keywords: alcohol, TsOH, etherification, ether



- a: R₁=R₂=Ph
- b: R₁=Ph; R₂=2-ClC₆H₄
- c: R₁=Ph; R₂=4-BrC₆H₄
- d: R₁=Ph; R₂=2-NO₂C₆H₄
- e: R₁=Ph; R₂=2-MeC₆H₄
- f: R₁=Ph; R₂=3-MeC₆H₄
- g: R₁=Ph; R₂=4-MeC₆H₄
- h: R₁=R₂=4-MeC₆H₄

Experimental procedures:

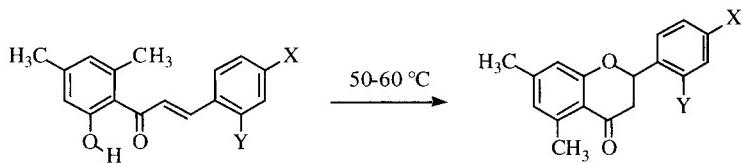
A mixture of powdered 4-methylbenzhydrol **1g** and an equimolar amount of TsOH was kept at room temperature for 10 min, and the reaction mixture was extracted with ether. The ether solution was worked up by the usual method and distillation of the crude product gave the corresponding ether **2g** in 96% yield.

References: F. Toda, H. Takumi, M. Akehi, *Chem. Commun.*, 1270 (1990).

Type of reaction: C–O bond formation

Reaction condition: solid-state

Keywords: 2'-hydroxy-4',6'-dimethylchalcone, Michael-type addition, flavanone



- a: X=H; Y=H

- b: X=Cl; Y=H

- c: X=Br; Y=H

- d: X=H; Y=Cl

Experimental procedures:

Finely powdered chalcones (100–500 mg) were heated at 50–60 °C with occasional stirring for 7–20 days. Chalcones **1a–c** were found to gradually change their color during heating but chalcone **1d** remained stable. The flavanones **2a–c**

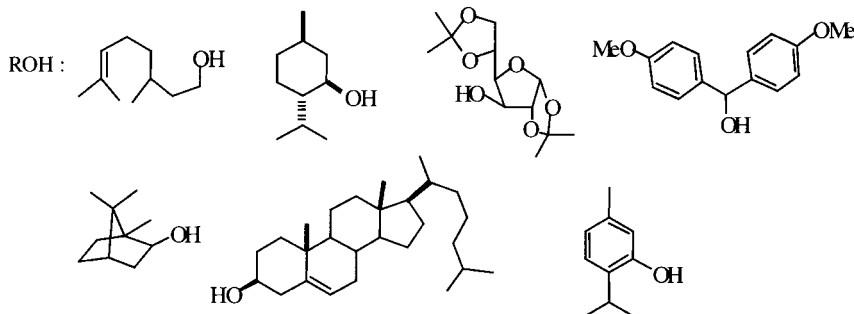
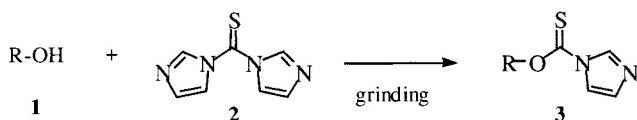
were separated from the reaction mixtures by column chromatography (silica gel, hexane-5% EtOAc) in nearly 70% isolated yield. All products were characterized by NMR and IR spectroscopy and also compared with the authentic samples.

References: B. S. Goud, K. Panneerselvam, D. E. Zacharias, G. R. Desiraju, *J. Chem. Soc., Perkin Trans. 2*, 325 (1995).

Type of reaction: C–O bond formation

Reaction condition: solid-state

Keywords: thiocarbonylimidazole, alcohol, thiocarbonylimidazolide



Experimental procedures:

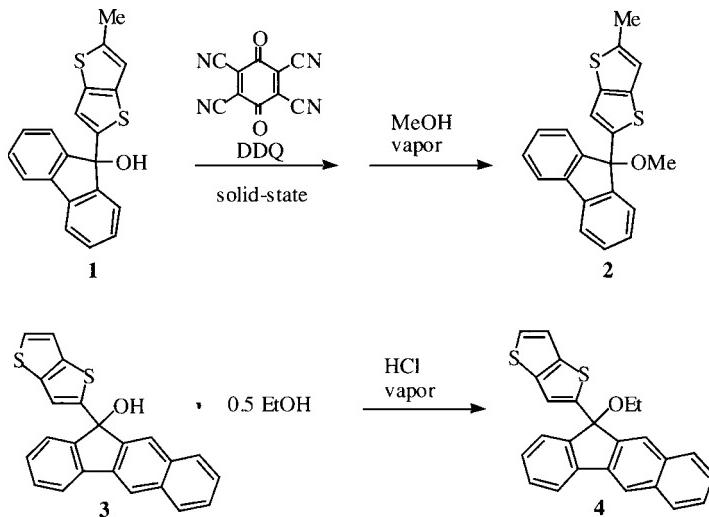
A mixture of alcohol **1** and 1.2 equiv. of thiocarbonylimidazole **2** in a mortar was ground well with a pestle at room temperature in ambient atmosphere. Progress of the reaction was monitored by TLC using a glass capillary tube which kept ethanol inside beforehand. In some cases, termination of the reaction was indicated by liquefaction of solid. After grinding occasionally for 2–3 h, the resulting mixture was dissolved in ethyl acetate. The solution was passed through a short column of silica gel. Evaporation of the solvent followed by purification of the residue by medium pressure liquid chromatography provided thiocarbonylimidazolide **3**.

References: H. Hagiwara, S. Ohtsubo, M. Kato, *Tetrahedron*, **53**, 2415 (1997).

Type of reaction: C–O bond formation

Reaction condition: solid-state

Keywords: 9-thienothienylfluoren-9-ol, DDQ, gas-solid reaction, etherification



Experimental procedures:

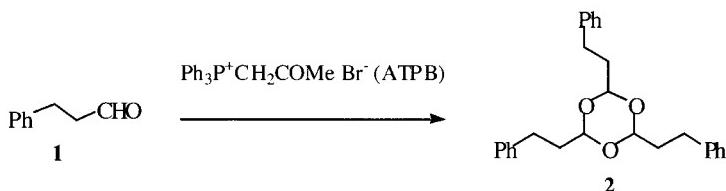
The substrate (10–20 mg, ca. 0.04 mmol) was coground with ca. 9.1 mg (0.04 mmol) of DDQ in a mortar with a pestle for about 10 min. The resulting colored solids were transferred to a small vial without a cap, and it was placed in a closed vessel, in which a shallow pool of methanol (1 mL) was maintained at the bottom. The vessel was kept in a refrigerator for 5–10 h. Product analysis was carried out by means of the ¹H NMR spectra for the sample after working up with a saturated NaHCO₃ solution.

References: M. Tanaka, K. Kobayashi, *Chem. Commun.*, 1965 (1998); M. Tanaka, N. Tanimoto, K. Kobayashi, *J. Org. Chem.*, **66**, 803 (2001).

Type of reaction: C–O bond formation

Reaction condition: solvent-free

Keywords: 3-phenylpropionaldehyde, acetyltri phenylphosphonium bromide, cyclotrimerization

**Experimental procedures:**

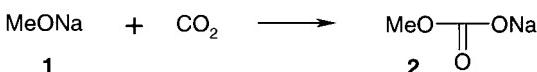
A mixture of the 3-phenylpropionaldehyde **1** (385 mg, 2.87 mmol) and ATPB (115 mg, 0.287 mmol) was stirred at room temperature for 24 h. The crude mixture were subjected to silica gel column chromatography to isolate the desired product **2** (300 mg) in 78% yield.

References: Y. Hon, C. Lee, *Tetrahedron*, **57**, 6181 (2001).

Type of reaction: C–O bond formation

Reaction condition: solid-state

Keywords: alcoholate, CO_2 , large scale, carboxylation, gas-solid reaction, carbonic acid half ester salts

**Experimental procedures:**

A chromatography column (diameter 4 cm, height 60 cm) with a D3-frit and gas outlet through a drying tube was charged upon glass wool with commercial 97.5% **1** (250 g, 4.63 mol) or 95% **3** (250 g, 3.68 mol) or 95% **5** (250 g, 2.23 mol) and covered with glass wool. Initially a mixture of CO_2 (250 mL min⁻¹) and N_2 (2.25 L min⁻¹) was applied from the bottom. It created a warm zone of about 50°C that passed the column in about 1 h. After that, the N_2 -stream was halved and the reaction continued until the heat production ceased and such halving was repeated twice again. Finally the N_2 -flow was removed and the now cold column left closed with pure CO_2 overnight. The weight in-

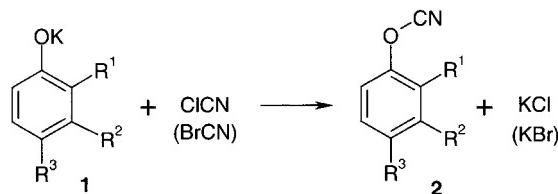
crease (without correction for losses due to initially present ROH contents) was 191 g (97%), 154 g (95%) and 90 g (92%), and the fill volume increase 29, 45 and 56%, respectively. The pH values of aqueous solutions of the products varied from 8.5 to 9. Titration after decomposition with aqueous H₂SO₄ gave content values between 97 and 102% of the versatile reagents **2**, **4**, or **6** for alkylations, carboxylations and acylations.

References: G. Kaupp, D. Matthies, C. de Vrese, *Chem. Ztg.*, **113**, 219 (1989); G. Kaupp, *Merck Spectrum*, **3**, 42–45 (1991).

Type of reaction: C–O bond formation

Reaction condition: solid-state

Keywords: phenolate, cyanogen chloride, cyanogen bromide, cyanate, gas-solid reaction



a: R¹=R²=H, R³=OMe

b: R¹=H, R²=R³=OMe

c: R¹=R²=H, R³=CHO

d: R¹=NO₂, R²=R³=H

Experimental procedures:

Solid potassium 4-methoxyphenolate **1a** (10 mmol) was treated with CICN (1 bar, 11.2 mmol) or with BrCN (1.17 g, 11.0 mmol from a remote flask at a vacuum line) and left overnight. Excess gas was recovered in a cold trap. KCl (KBr) was washed away with water and the quantitatively obtained product **2a** dried in a vacuum.

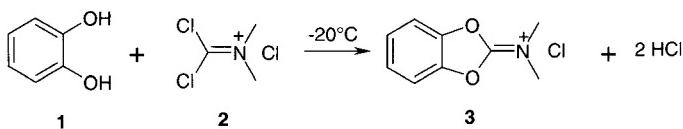
Similarly, the aryl cyanates **2b–d** were quantitatively obtained.

References: G. Kaupp, J. Schmeyers, J. Boy, *Chem. Eur. J.*, **4**, 2467 (1998).

Type of reaction: C–O bond formation

Reaction condition: solid-state

Keywords: Viehe salt, pyrocatechol, solid-solid reaction, keteneiminium salt

**Experimental procedure:**

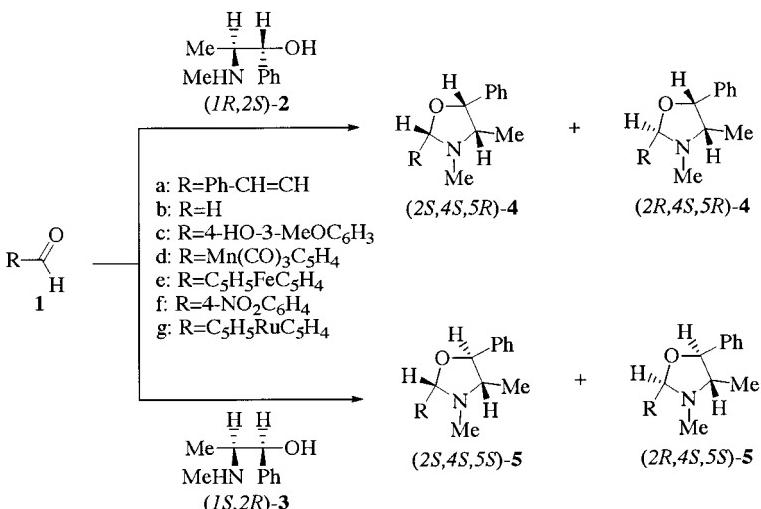
Solid pyrocatechol **1** (550 mg, 5.00 mmol) and Viehe salt **2** (815 mg, 5.00 mmol) were ball-milled at -20°C for 1 h. Most of the liberated HCl escaped through the Teflon gasket that was tightened against a torque of 50 Nm. Residual HCl was pumped off at room temperature. The yield of **3** was 998 mg (100%).

References: G. Kaupp, J. Boy, J. Schmeyers, *J. Prakt. Chem.*, **340**, 346 (1998).

Type of reaction: C–O bond formation

Reaction condition: solid-state

Keywords: aldehyde, (−)-ephedrine, (+)-pseudoephedrine, optically active oxazolidine

**Experimental procedures:**

After an enantiomerically pure β -amino alcohol (1 mmol) had been mixed with the appropriate aldehyde (1 mmol) the mixture was kept in the dark at room temperature and periodically stirred. The course of the reaction was monitored regu-

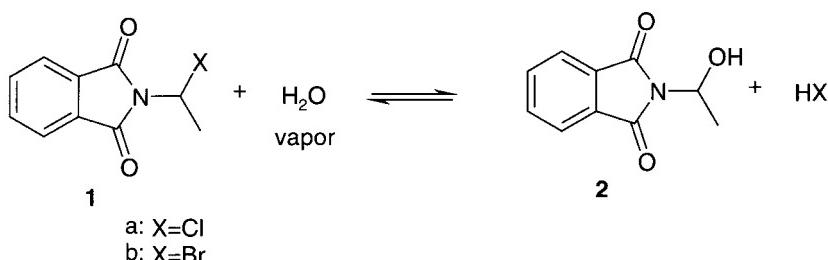
larly by recording the NMR spectra of samples of the reaction mixture. In all cases the yield of the products was 100%.

References: N.S. Khruscheva, N.M. Loim, V.I. Solkolov, V.D. Makhaev, *J. Chem. Soc., Perkin Trans. 1*, 2425 (1997).

Type of reaction: hydrolysis

Reaction condition: solid-state

Keywords: phthalimide, substitution, gas-solid reaction



Experimental procedures:

Compound **1a** (100 mg, 0.47 mmol) or **1b** (100 mg, 0.39 mmol) was placed on a glass frit and moist air was sucked through by an aspirator for 2 h. The slightly wetish crystals were dried in a high vacuum and consisted of pure **2** according to ^1H NMR analysis.

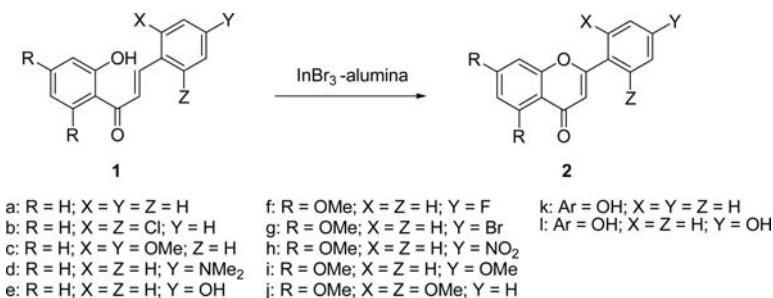
The reaction is reversible: If an excess of HX gas was applied to **2** the pure compound **1a** or **1b** was obtained.

References: G. Kaupp, D. Matthies, *Chem. Ber.*, **119**, 2387 (1986).

Type of reaction: C–O bond formation

Reaction condition: solvent-free

Keywords: 2'-hydroxychalcone, flavanone, silica gel

**Experimental procedures:**

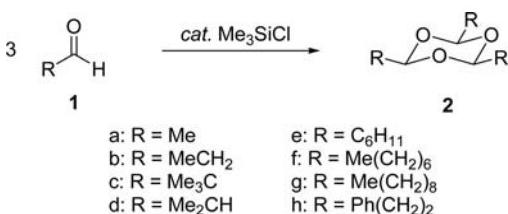
The 2'-hydroxychalcones or flavanones (1.0 mmol, dissolved in a minimum amount of ethyl acetate) were added to silica gel supported InBr₃ (2.0 g, 15–20 mol%) and the solvent was removed. The dry mixture was heated with stirring at 130–140 °C in an inert container for different periods of time. The reaction mixture was directly applied onto a silica gel column and eluted with a mixture of ethyl acetate–hexane (1:1).

References: N. Ahmed, H. Ali, J.E. van Lier, *Tetrahedron Lett.*, **46**, 253 (2005).

Type of reaction: C–O bond formation

Reaction condition: solvent-free

Keywords: trioxane, trimerization, aldehyde, trimethylsilyl chloride

**Experimental procedures:**

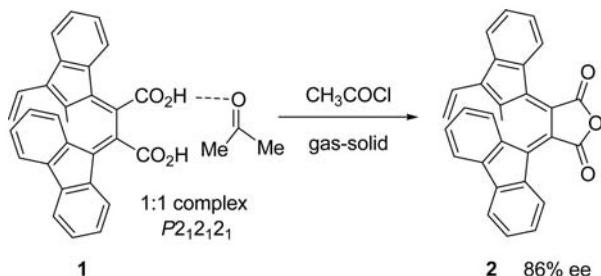
In a typical experiment, 0.004 equiv. of trimethylsilyl chloride was added under stirring to the liquid aldehyde. The mixture was allowed to stand overnight under argon. It was then evaporated to remove TMSCl. The solid residue was eventually recrystallized from ethanol.

References: J. Augè, R. Gil, *Tetrahedron Lett.*, **43**, 7919 (2002).

Type of reaction: C–O bond formation

Reaction condition: gas-solid

Keywords: 2,3-bis-fluoren-9-ylidenesuccinic acid, chiral crystal



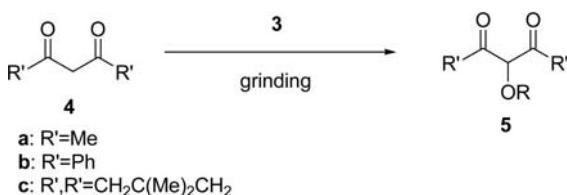
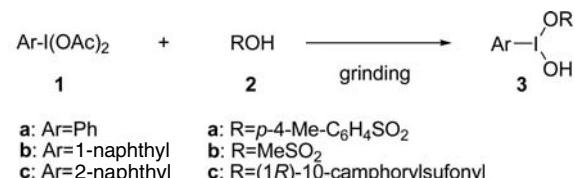
Experimental procedures: A crystalline powder of an optically active inclusion complex of (+)-**1** and acetone was treated with gaseous acetyl chloride in a desiccator for 3 days at room temperature. The crude product was washed with water and then dried to give optically active 2,3-bis(fluorenylidene)succinic anhydride **2** in 85% yield.

References: K. Tanaka, T. Iwamoto, S. Wada, J. Frelek, M. R. Caira, *Chirality*, **18**, 483 (2006).

Type of reaction: C–O bond formation

Reaction condition: solvent-free

Keywords: hypervalent iodine, sulfonylation, 1,3-diketone



Experimental procedures:

Methanesulfonic acid **2b** (92 mg, 0.96 mmol) and (diacetoxyiodo)benzene **1a** (302 mg, 0.94 mmol) were placed in an agate mortar and intensively ground. The formation of acetic acid was observed and the reaction mass turned yellow. After approximately 1 min the color of the reaction mixture changed to white and the formation of white crystals was observed. The grinding was continued for

10 min. The product was dried in high vacuum to remove the residue of acetic acid and methanesulfonic acid to yield **3b** (292 mg, 98%).

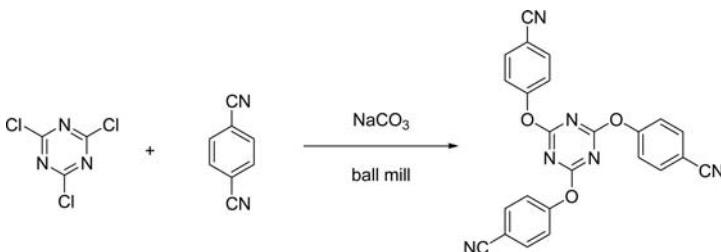
Hydroxy(tosyloxy)iodobenzene **3a** or hydroxy(methansulfonyl)iodobenzene **3b** and the corresponding ketone **4** were ground in an agate mortar for 10 min. The resulting mass formed a thin layer on the surface of the mortar. All this mass was moved to the center of the bottom of the mortar and the grinding was repeated for 10 min. The reaction mixture was dried under high vacuum and the residue washed with a small amount of diethyl ether.

References: M. S. Yusubov, T. Wirth, *Org. Lett.*, **7**, 519 (2005).

Type of reaction: C–O bond formation

Reaction condition: solvent-free

Keywords: 2,4,6-tris(4-cyanophenoxy)-1,3,5-triazine, ball-mill



Experimental procedures:

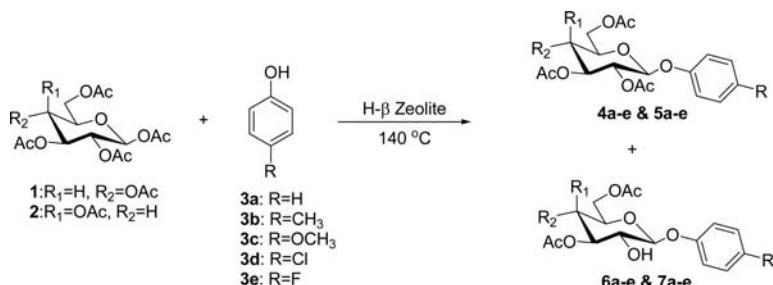
0.92 g (0.005 mol) cyanur chloride and 2.08 g (0.017 mol) 4-cyanophenol and excess of NaCO₃ were mixed and ground in a ball mill for 2 days with continuous breaks (repeated cycles of 5 h milling followed by 30 min break). The raw material was thoroughly washed with a large amount of water and recrystallized from chloroform. Yield: 80.1%.

References: H. I. Suss, A. Neels, J. Hulliger, *CrystEngComm*, **7**, 370 (2005).

Type of reaction: C–O bond formation

Reaction condition: solid state

Keywords: carbohydrate, aryl C-2-hydroxy-glycoside, H- β zeolite



Experimental procedures:

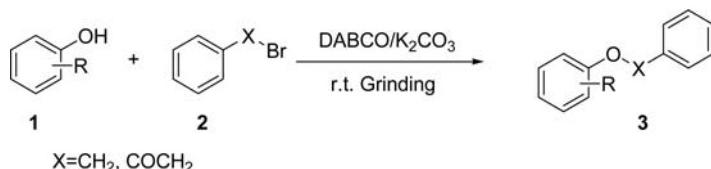
A mixture of sugar peracetate (**1** or **2**, 1.0 mmol) and phenol (**3,5** mmol) in a 100 ml round-bottom flask was heated to ~100°C in a silicone oil bath. Freshly activated H-zeolite (200 mg) was added to the melt obtained. The resulting mixture was magnetically stirred and the temperature raised to 140°C. The progress of the reaction was monitored by TLC (EtOAc–hexane, 1:2). Following completion of the reaction (10–16 h), the reaction mixture was cooled to room temperature, diluted with chloroform (50 mL) and heated at reflux for 1.5 h to extract the product from the zeolite pores. The catalyst was then filtered. This extraction procedure was repeated twice. The combined filtrate was concentrated to give a residue that was subjected to flash column chromatography over silica gel using a mixture of EtOAc and hexane as the eluent to furnish the title compounds.

References: U. Aich, D. Loganathan, *Carbohydrate Res.*, **341**, 19 (2006).

Type of reaction: C–O bond formation

Reaction condition: solvent-free

Keywords: phenol, *O*-alkylation



Experimental procedures:

The corresponding phenols (5 mmol), anhydrous K₂CO₃ (6.5 mmol), organic base (0.125 mmol) and alkyl bromides (5 mmol) were mixed in a mortar and ground intermittently using a pestle. The mixture changed to a mushy state within an appropriate reaction time and then solidified. The reaction was monitored with TLC. Once the reaction was complete, the crude products were purified by silica gel chromatography using hexane–ethyl acetate as eluent. All obtained

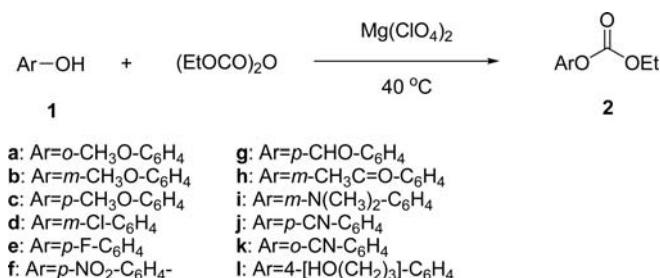
compounds were characterized by ^1H NMR, ^{13}C NMR, MS (FAB), and elemental analysis.

References: X. Bu, H. Jing, L. Wang, T. Chang, L. Jin, Y. Liang, *J. Mol. Cat. A: Chemical*, **259**, 121 (2006).

Type of reaction: C–O bond formation

Reaction condition: solvent-free

Keywords: alkyl aryl carbonate, magnesium perchlorate



Experimental procedures:

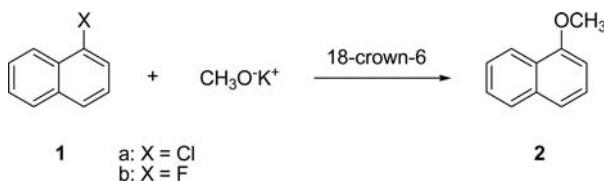
To a two-necked flask equipped with a magnetic stirring bar, $\text{Mg}(\text{ClO}_4)_2$ (0.1 mmol), the phenol **1** (1.0 mmol) and diethyl dicarbonate **2** (1.2 mmol) were added. The mixture was stirred at 40°C until the GC-MS analysis revealed the presence of **1**. The crude reaction mixture was diluted with water and extracted with Et_2O . The organic layer was separated, dried with MgSO_4 and filtered, and the solvent was removed by rotary evaporation. The aryl ethyl carbonate **2** was purified by flash chromatography on silica gel with a mixture of petroleum ether– $\text{Et}_2\text{O}=95:5$.

References: G. Bartoli, M. Bosco, A. Carloni, M. Locatelli, E. Marcantoni, P. Melchiorre, P. Palazzi, L. Sambri, *Eur. J. Org. Chem.*, 4429 (2006).

Type of reaction: C–O bond formation

Reaction condition: solvent-free

Keywords: aromatic ether, aromatic nucleophilic substitution



Experimental procedures:

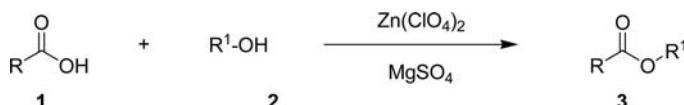
18-Crown-6 (0.5 mmol, 10%) was added to the aromatic substrate (5 mmol) and potassium alkoxide (7.5 mmol). The mixture was introduced into a Pyrex vessel adapted to the microwave equipment (Synthewave 402 monomode reactor from Prolabo) fitted with a mechanical stirrer. S402 software permitted programming in time and monitoring of the temperature by modulation of the power from 15 to 300 W. Irradiation was carried out according to the conditions indicated in the Tables. At the end of the reaction, the organic products were extracted into diethyl ether, and filtration through Celite 545 was carried out. The products were identified (GC-MS, NMR) by comparison with authentic samples and analyzed by GC (internal standard = *a*-naphthol).

References: M. Chaouchi, A. Loupy, S. Marque, A. Petit, *Eur. J. Org. Chem.*, 1278 (2002).

Type of reaction: C–O bond formation

Reaction condition: solvent-free

Keywords: esterification, zinc perchlorate



R: PhCH₂CH₂, *c*-C₆H₁₁, 1-adamantyl, Ph, (*E*)-PhCH=CH, Boc-NH(CH₂)₁₀, CH₂=CH(CH₂)₂, BrCH₂CH₂, CH₃COCH₂CH₂, CH₃(CH₂)₇

R': CH₃(CH₂)₇, CH₃(CH₂)₅(CH₃)CH, PhCH₂, (*E*)-CH₃CH₂CH=CHCH₂CH₂, (*Z*)-CH₃CH₂CH=CHCH₂CH₂, PhCH₂O(CH₂)₄.

Experimental procedures:

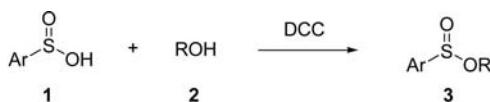
An oven-dried Schlenk tube was charged with Zn(ClO₄)₂·6H₂O (18.6 mg, 0.05 mmol), MgSO₄ (120 mg, 1 mmol), 1-octanol (157 L, 1 mmol), 3-phenylpropanoic acid (165 mg, 1.1 mmol), and immersed up to the top in an oil bath at 80 °C. The mixture was stirred for 8 h, then cooled to room temperature, and diluted with CH₂Cl₂. The catalyst was filtered off, and the organic layer was washed with water, then aqueous NaHCO₃. After drying with MgSO₄ and evaporation of the solvent, the crude product was purified by flash chromatography on a silica gel column (petroleum ether–diethyl ether, 4:1) to give the desired carboxylic ester; yield: 249 mg (95%). The filtered catalyst was reactivated by heating in an oven at 60 °C overnight and reused.

References: G. Bartoli, J. Boeglin, M. Bosco, M. Locatelli, M. Massaccesi, P. Melchiorre, L. Sambri, *Adv. Synth. Catal.*, **347**, 33 (2005).

Type of reaction: C–O bond formation

Reaction condition: solvent-free

Keywords: sulfinate ester, DCC, sulfinic acid



- | | |
|--|---|
| a: Ar=p-CH ₃ C ₆ H ₄ , R=CH ₃ | i: Ar=p-CH ₃ C ₆ H ₄ , R=CH ₃ (CH ₂) ₆ CH ₃ |
| b: Ar=p-CH ₃ C ₆ H ₄ , R=CH ₃ CH ₂ | g: Ar=p-CH ₃ C ₆ H ₄ , R=1-Adamantanyl |
| c: Ar=p-CH ₃ C ₆ H ₄ , R=CH ₃ (CH ₂) ₂ | h: Ar=p-CH ₃ C ₆ H ₄ , R=(CH ₃) ₃ C |
| d: Ar=p-CH ₃ C ₆ H ₄ , R=CH ₃ (CH ₂) ₃ | i: Ar=p-CH ₃ C ₆ H ₄ , R=C ₆ H ₄ (CH ₂) ₄ |
| e: Ar=p-CH ₃ C ₆ H ₄ , R=CH ₃ CH(CH ₃)CH ₂ | j: Ar=p-CH ₃ C ₆ H ₄ , R=p-MeOC ₆ H ₄ CH ₂ |
| f: Ar=p-CH ₃ C ₆ H ₄ , R=CH ₃ (CH ₂) ₂ CH(CH ₃) | k: Ar=p-CH ₃ C ₆ H ₄ , R=m-MeOC ₆ H ₄ CH ₂ |
| g: Ar=p-CH ₃ C ₆ H ₄ , R=Cyclohexyl | l: Ar=p-CH ₃ C ₆ H ₄ , R=p-ClC ₆ H ₄ CH ₂ |
| h: Ar=p-CH ₃ C ₆ H ₄ , R=C ₆ H ₅ CH ₂ | m: Ar=C ₆ H ₅ , R=Me |
| i: Ar=p-CH ₃ C ₆ H ₄ , R=C ₆ H ₅ CH ₂ CH ₂ | n: Ar=p-MeOC ₆ H ₄ , R=L-Menthyl |
| j: Ar=p-CH ₃ C ₆ H ₄ , R=L-Menthyl | o: Ar=p-ClC ₆ H ₄ , R=L-Menthyl |
| k: Ar=p-CH ₃ C ₆ H ₄ , R=ClCH ₂ CH ₂ | p: Ar=p- ^t BuC ₆ H ₄ , R=L-Menthyl |

Experimental procedures:

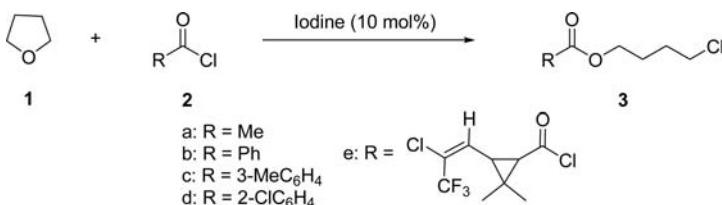
A mortar was charged with the alcohol (1 mmol), *p*-toluenesulfinic acid (1 mmol, 0.16 g), and DCC (1 mmol, 0.21 g). The reaction mixture was ground with a pestle in the mortar for the time specified in Table 1. When TLC showed no remaining toluenesulfinic acid (EtOAc–n-hexane, 15:85), H₂O (5 mL) was added to the reaction mixture and extracted with ether (2×10 mL) and the combined ethereal layer was washed with saturated NaHCO₃, dried (MgSO₄) and the ether was evaporated to dryness using a rotary evaporator. The residue was purified by column chromatography using silica gel and a mixture of n-hexane–EtOAc (85:15) to give the pure product.

References: A. R. Hajipour, A. R. Falahati, A. E. Ruoho, *Tetrahedron Lett.*, **47**, 2717 (2006).

Type of reaction: C–O bond formation

Reaction condition: solvent-free

Keywords: iodine, ether



Experimental procedures:

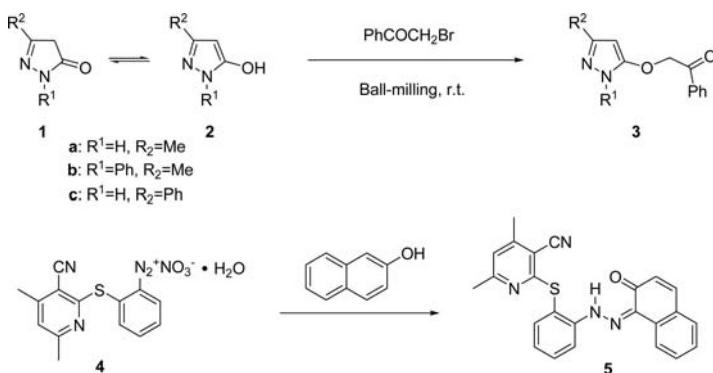
To a mixture of cyclic ether (6.90 mmol) and acyl chloride (0.69 mmol), a catalytic amount of iodine (10 mol%) was added. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for an appropriate time. After completion of the reaction, as indicated by TLC, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (15 mL) and extracted with ethyl acetate (2×15 mL). Evaporation of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, (0.5:9.5) afforded the pure ester derivatives.

References: J.S. Yadav, B.V.S. Reddy, P.M.K. Reddy, M.K. Gupta, *Tetrahedron Lett.*, **46**, 8493 (2005).

Type of reaction: C–O bond formation

Reaction condition: solid-state

Keywords: thiazole, azo-coupling, ball-milling

**Experimental procedures:**

A mixture of **1** or **2** (2.00 mmol) and phenacyl bromide (398 mg, 2.00 mmol) was ball-milled at room temperature for 1 h. The solid powders were washed with 5% Na₂CO₃ solution, followed by H₂O, and dried at 0.01 bar at 80 °C in vacuum to liberate the free ethers **3**.

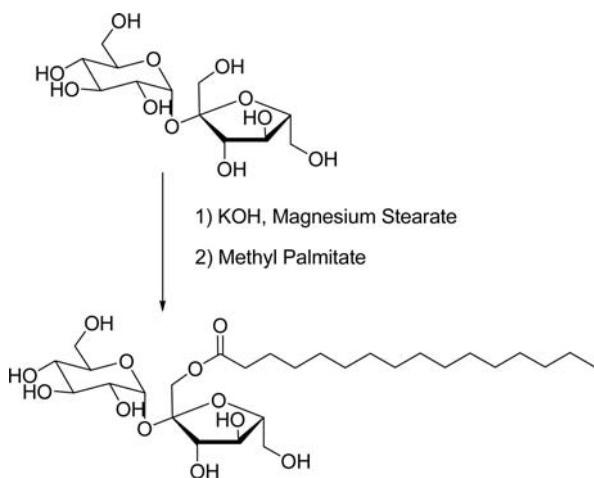
β -Naphthol (288 mg, 2.00 mmol) was ground in an agate mortar, and **4** (694 mg, 3.00 mmol) were added and co-ground in five portions for 10 min each. Most of the diazonium band at $\nu=2292\text{ cm}^{-1}$ disappeared, but the completion of the reaction was achieved by 24 h ultrasound application in a test tube. The solid product was neutralized with 20 mL 0.5 N NaOH, washed with H₂O, and dried. Mp 157–158 °C.

References: E. Abdel-Latif, M.A. Metwally, *Monatsh. Chem.*, **138**, 771 (2007).

Type of reaction: C–O bond formation

Reaction condition: solvent-free

Keywords: sucrose ester, co-melting, magnesium stearate



Experimental procedures:

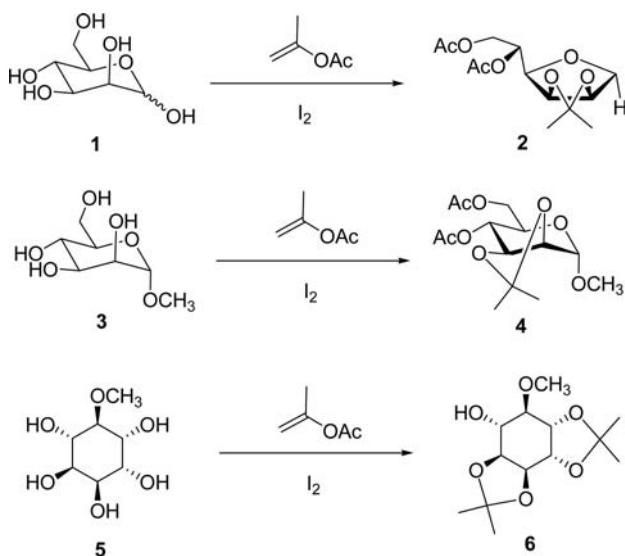
In a 500 mL mixer with counter-rotating blades, sucrose (100 g), base, soap and 0–20 mL of water were mixed together at 75–100 °C for 1 h. The mixture was dried under vacuum for 30–60 min and then melted methyl palmitate was added. The mixture was allowed to react under vacuum at 125–135 °C, for 3–8 h.

References: J. Fitremann, Y. Queneau, J.-P. Maitre, A. Bouchu, *Tetrahedron Lett.*, **48**, 4111 (2007).

Type of reaction: C–O bond formation

Reaction condition: solvent-free

Keywords: isopropylidination, iodine, mannose



Experimental procedures:

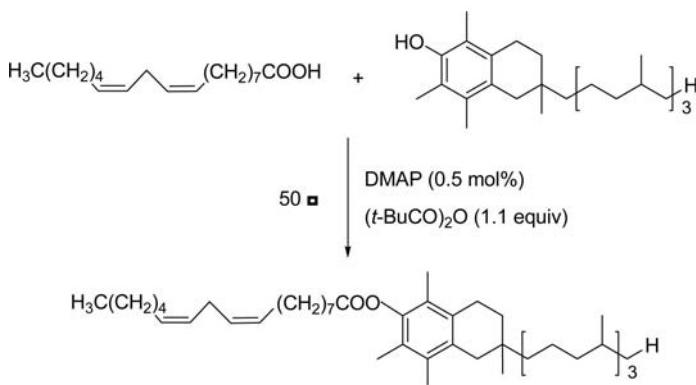
Molecular iodine (0.1 mmol) was added to a suspension of D-mannose (180 mg, 1 mmol) and IPA (400 mg, 4 mmol) at -20°C and the mixture was stirred at room temperature under nitrogen atmosphere. After the reaction was complete (TLC), it was extracted with dichloromethane (20 mL) and washed with saturated sodium thiosulfate solution (4 mL). The organic layer was dried over sodium sulfate, evaporated to dryness, and subjected to column chromatography on silica gel (100–200 mesh) by using petroleum ether (60–80) with increasing proportions of ethyl acetate (1–15%) to afford 1,4,6-tri-*O*-acetyl-2,3-*O*-isopropylidene-D-mannopyranose **2** (280 mg, 81%) as the major product.

References: D. Mukherjee, B.A. Shah, P. Gupta, S.C. Taneja, *J. Org. Chem.*, **72**, 8965 (2007).

Type of reaction: C–O bond formation

Reaction condition: solvent-free

Keywords: 4-(*N,N*-dimethylamino)pyridine, esterification

**Experimental procedures:**

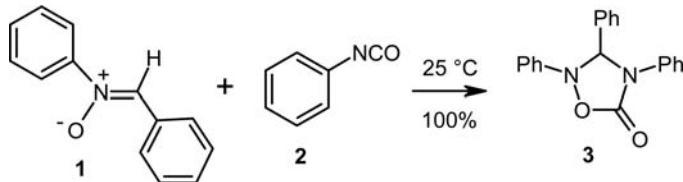
To a mixture of α -tocopherol (2.15 g, 5.0 mmol), linoleic acid (1.71 mL, 5.5 mmol), and DMAP (3.1 mg, 0.025 mmol) was added pivalic anhydride (1.07 mL, 5.5 mmol) at ambient temperature. After stirring at 50 °C for 27 h, water (9 mL, 0.5 mmol) was added and the mixture was stirred at 50 °C for 1 h. The resultant mixture was concentrated under reduced pressure (ca. 0.0006 Torr) at 90 °C (bath temperature) to recover the generated pivalic acid. The residue was passed through a short silica gel pad (10 g) using a mixture of hexane and ethyl acetate (100:1, 60 mL), to give α -tocopherol linoleate (3.05 g, 88% yield).

References: A. Sakakura, K. Kawajiri, T. Ohkubo, Y. Kosugi, K. Ishihara, *J. Am. Chem. Soc.*, **129**, 14775 (2007).

Type of reaction: C–O bond formation

Reaction condition: solid-state

Keywords: gas-solid reaction, 1,3-dipolar addition, diphenylnitrone, phenylisocyanate, 1,2,4-oxadiazolidine-5-one, quantitative, stereospecific

**Experimental procedure:**

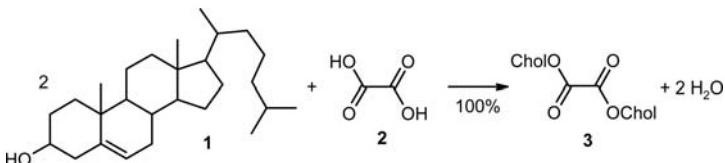
Freshly distilled phenylisocyanate **2** (238 mg, 2.00 mmol) in an evacuated 50-mL flask at 60 °C was connected to an evacuated 50-mL flask with the nitrone **1** (394 mg, 2.00 mmol) at 70 °C. The vacuum tight arrangement was left at these temperatures for 5 h to obtain pure 2,3,4-triphenyl-1,2,4-oxadiazolidine-5-one **3**, mp 168 °C in quantitative yield.

References: G. Kaupp, *Top. Curr. Chem.*, **254**, 95 (2005).

Type of reaction: C–O bond formation

Reaction condition: solid-state

Keywords: solid-solid reaction, quantitative, cholesterol, oxalic acid, esterification, esterification, ball mill



Experimental procedure:

Cholesterol **1** (773 mg, 2.00 mmol) and oxalic acid **2** (90 mg, 1.00 mmol) were ball-milled at 90 °C for 1 h to give a quantitative yield of diester **3** that was dried *in vacuo* at 100 °C.

Alternatively, the same components were ball-milled at room temperature for 10 min and the mixture of the 1:1-complex **1·2** and **1** heated to 100 °C for 1 h in an open vessel to obtain pure **3** in quantitative yield.

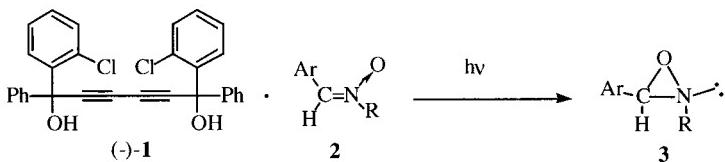
References: G. Kaupp, Waste-free synthesis and production all across chemistry with the benefit of self-assembled crystal packings, *J. Phys. Org. Chem.*, **2008**, 21, DOI 10.1002/poc.1340.

5.2 Solvent-Free C–O Bond Formation under Photoirradiation

Type of reaction: C–O bond formation

Reaction condition: solid-state

Keywords: nitrone, photocyclization, inclusion complex, oxaziridine



- a: Ar=Ph; R=*i*-Pr
- b: Ar=Ph; R=*t*-Bu
- c: Ar=4-ClC₆H₄; R=*t*-Bu
- d: Ar=2-ClC₆H₄; R=*t*-Bu
- e: Ar=3,4-CH₂O₂C₆H₃; R=*i*-Pr
- f: Ar=3,4-CH₂O₂C₆H₃; R=*t*-Bu
- g: Ar=Ph; R=*i*-PrMeCH

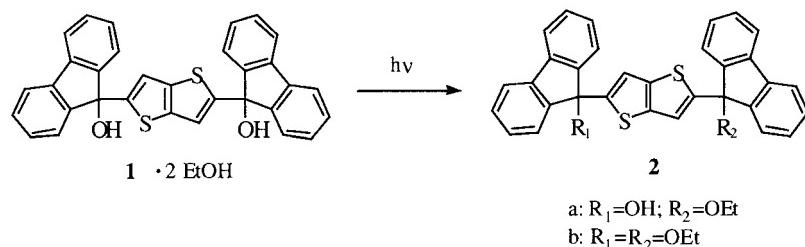
Experimental procedures:

The 1:1 inclusion complex of (–)–**1** and **2a** was powdered and irradiated by a high pressure Hg-lamp for 24 h at room temperature, and the reaction mixture was chromatographed on silica gel (benzene) to give (+)–**3** in 56% yield.

References: F. Toda, K. Tanaka, *Chem. Lett.*, 2283 (1987).

Type of reaction: C–O bond formation**Reaction condition:** solid-state

Keywords: bis(9-hydroxyfluoren-9-yl)thieno[3,2-*b*]thiophene, clathrate, photosolvolytic, etherification

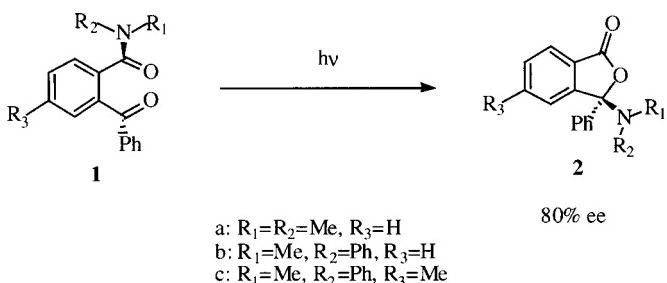
**Experimental procedures:**

Upon recrystallization from ethanol **1** afforded the clathrate crystal with a host-guest molar ratio of 1:2. Grinded **1**·2EtOH crystals were irradiated by means of a high-pressure mercury lamp at ambient temperature for 6 h. The photoproducts were chromatographed on a silica gel column to give monoether **2a** (43%) and diether **2b** (21%) along with unreacted **1** (36%).

References: N. Hayashi, Y. Mazaki, K. Kobayashi, *Tetrahedron Lett.*, **35**, 5883 (1994).

Type of reaction: C–O bond formation**Reaction condition:** solid-state

Keywords: 2-benzoylbenzamide, absolute asymmetric synthesis, single-crystal-to-single-crystal reaction, photoirradiation, 3-(*N*-methylanilino)-3-phenylphthalide



Experimental procedures:

Solid samples placed in the bottom of the test tube were cooled in a cooling apparatus and were irradiated by Pyrex-filtered light transmitted by using a flexible light guide from a 250-W ultra-high-pressure mercury lamp. When the powdered **1b** was irradiated at 15 °C for 2 h, a quantitative amount of 3-(*N*-methylanilino)-3-phenylphthalide **2b** ($[\alpha]_D^{21} 21^\circ$ (*c* 1.0, CHCl₃)) was obtained.

References: M. Sakamoto, N. Sekine, H. Miyoshi, T. Mino, T. Fujita, *J. Am. Chem. Soc.*, **122**, 10210 (2000).

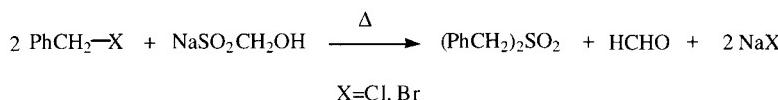
6 Carbon–Sulfur Bond Formation

6.1 Solvent-Free C–S Bond Formation

Type of reaction: C–S bond formation

Reaction condition: solvent-free

Keywords: sodium dithionite, sodium formaldehyde sulfoxylate, benzyl halide, dibenzyl sulfone



Experimental procedures:

Benzyl bromide (17.1 g, 0.1 mol) was added to a mixture of solid sodium dithionite (10.44 g, 0.06 mol) and Aliquat 336 (1.2 g, 0.03 mol). The mixture was vigorously shaken for 5 min and then heated in an oil bath for 20 h at 120 °C. Dibenzyl sulfone was removed by filtration through Florisil with 50 mL of methylene chloride. The solvent was evaporated and the crude solid crystallized from a 1:1 mixture of ethanol and toluene to give the pure sulfone as a white solid (7.54 g, 61%), mp 148–149 °C.

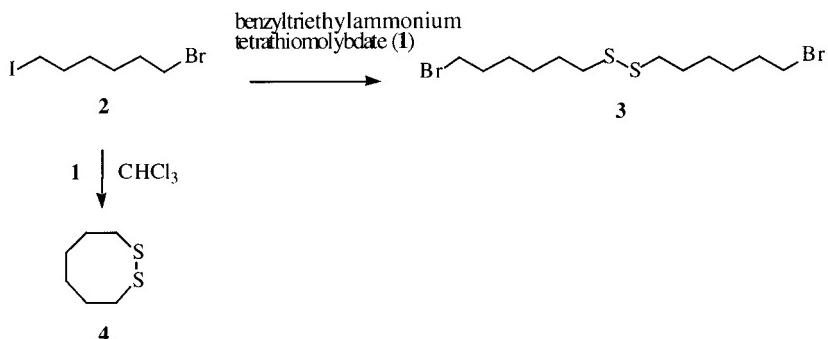
An analogous procedure was carried out with benzyl bromide (17.1 g, 0.1 mol), sodium formaldehyde sulfoxylate dihydrate (10.35 g, 0.06 mol) and sodium carbonate (10.35 g, 0.075 mol) to obtain the pure dibenzyl sulfone (9.35 g, 76% after recrystallization).

References: A. Loupy, J. Sansoulet, A.R. Harris, *Synth. Commun.*, **19**, 2939 (1989).

Type of reaction: C–S bond formation

Reaction condition: solid-state

Keywords: benzyltriethylammonium tetrathiomolybdate, alkyl halide, disulfide

**Experimental procedures:**

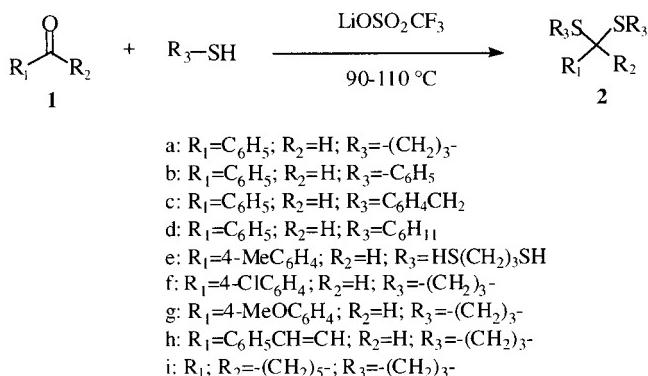
1-Bromo-6-iodohexane **2** (0.29 g, 1 mmol) was added in one portion to benzyltriethylammonium tetrathiomolybdate **1** (1.4 g, 2.2 mmol) in an agate mortar and the mixture was ground continuously for 5 min. The color of the mixture changed immediately from dark red to black and the initial viscous product became powdery within minutes. The mixture was ground occasionally for 20 min and then extracted with dichloromethane or diethyl ether; flash column chromatography of the extract on silica gel gave the product **3** as a viscous oil (0.1 g, 52%).

References: A. R. Ramesha, S. Chandrasekaran, *J. Chem. Soc., Perkin Trans. I*, 767 (1994).

Type of reaction: C–S bond formation

Reaction condition: solvent-free

Keywords: aldehyde, ketone, thiol, lithium trifluoromethanesulfonate, dithioacetalization, dithiane



Experimental procedures:

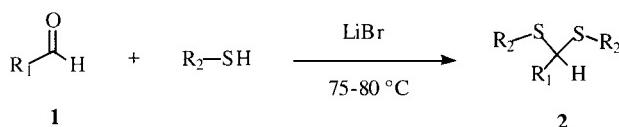
To a stirred mixture of the carbonyl compound (10 mmol) and dithiol (11–17 mmol) or monothiol (21 mmol), anhydrous LiOTf (0.5–3 mmol) was added. The mixture was heated at 90 °C (or 110 °C for ketones) while stirring was continued, and the progress of the reaction was followed by TLC. After completion of the reaction, CHCl₃ (100 mL) was added and the mixture was washed successively with 10% NaOH solution (2×25 mL), brine (15 mL), and water (15 mL). The organic layer was separated and dried over anhydrous Na₂SO₄. Evaporation of the solvent under reduced pressure gave almost pure product. Further purification was achieved by column chromatography on silica gel or recrystallization from an appropriate solvent to give the desired product in good to excellent yields. Most of the products are known and gave satisfactory physical data compared with those of authentic samples.

References: H. Firouzabadi, B. Karimi, S. Eslami, *Tetrahedron Lett.*, **40**, 4055 (1999).

Type of reaction: C–S bond formation

Reaction condition: solvent-free

Keywords: aldehyde, thiol, lithium bromide, dithioacetalization, 1,3-dithiane, 1,3-dithiolane



R₁=Ph, 4-MeC₆H₄, 3-MeC₆H₄, 3-ClC₆H₄, 4-ClC₆H₄, 4-MeOC₆H₄, 1-naphthyl, PhCH=CH

R₂=Ph, PhCH₂, c-C₆H₁₁, HS-(CH₂)₂-SH, HS-(CH₂)₃-SH

Experimental procedures:

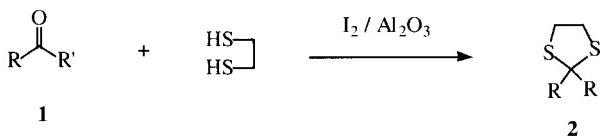
To a stirred mixture of the carbonyl compound **1** (10 mmol) and dithiol (11 mmol) or monothiol (20–21 mmol) was added anhydrous LiBr (2.5–4.0 mmol). The mixture was heated to 75–80 °C and the progress of the reaction was followed by TLC. After completion of the reaction (15–50 min), CH₂Cl₂ (100 mL) was added and the mixture was washed successively with 10% NaOH solution (2×25 mL), brine (15 mL), and H₂O (15 mL). The organic layer was separated and dried (Na₂SO₄). Evaporation of the solvent under reduced pressure gave almost pure product. Further purification was achieved by column chromatography on silica gel or recrystallization from appropriate solvent to give the desired products in good to excellent yields.

References: H. Firouzabadi, N. Iranpoor, B. Karimi, *Synthesis*, 58 (1999).

Type of reaction: C–S bond formation

Reaction condition: solvent-free

Keywords: ketone, aldehyde, ethane-1,2-dithiol, neutral alumina surface, dithioacetal, 1,3-dithiolane



- a: R=Ph; R'=H
- b: R=4-MeOC₆H₄; R'=H
- c: R=4-ClC₆H₄; R'=H
- d: R=4-NO₂C₆H₄; R'=H
- e: R=PhCH=CH; R'=H
- f: R=MeCH=CH; R'=H
- g: R=2-furyl; R'=H
- h: R=2-HOC₆H₄; R'=H
- i: R=C₁₆H₃₃; R'=H
- j: R=Me; R'=CH₂COOMe
- k: R=Ph; R'=Me
- l: R, R'=-(CH₂)₅-
- m: R= R=Ph

Experimental procedures:

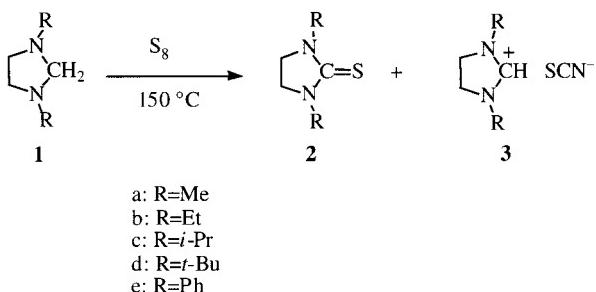
To a freshly prepared catalyst (1 g, 0.2 mmol of iodine) under stirring, a mixture of benzaldehyde **1a** (2 mmol) and ethane-1,2-dithiol (2.2 mmol) was added and stirring continued for 10 min or till the reaction was complete. For TLC monitoring, a small amount of the solid reaction mixture was taken out with a spatula and washed with a little amount of ethyl acetate to get a solution. On completion the reaction mixture was loaded on a short column of silica gel (60 to 120 mesh) and eluted with ethyl acetate. The organic layer was washed with a dilute solution of sodium thiosulfate followed by water and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure and purification of the residue by column chromatography yielded the pure product.

References: N. Deka, J.C. Sarma, *Chem. Lett.*, 794 (2001).

Type of reaction: C–S bond formation

Reaction condition: solvent-free

Keywords: aminal, sulfur, dehydrogenation, C–H activation, thiourea, carbenium thiocyanate



Experimental procedures:

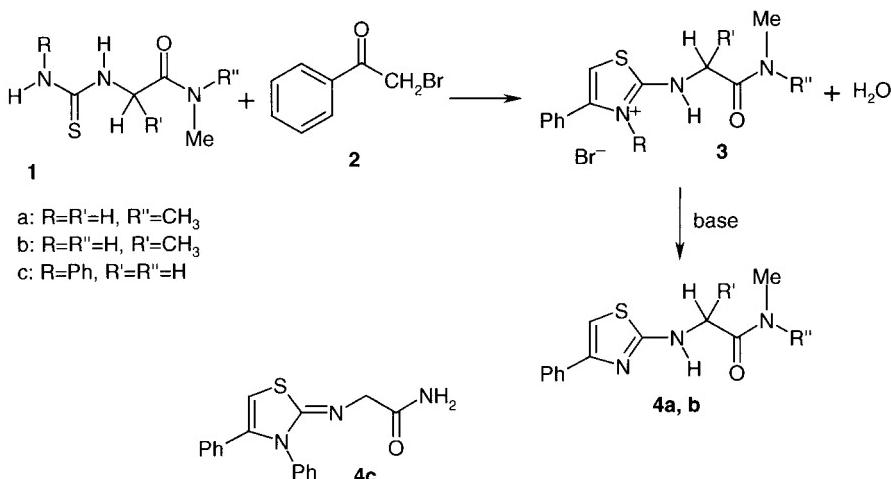
Sulfur (1.22 g, 4.75 mmol) was added to the aminal (19.0 mmol) in a Swagelock 50-mL stainless steel cylinder. The vessel was sealed and placed in an oil bath ($150\text{ }^\circ\text{C}$) for 12 h. The cold reaction mixture was extracted with methanol ($3 \times 10\text{ mL}$). The combined methanol extracts were filtered and the methanol was evaporated in vacuo. The thiourea were obtained by extraction of the solid residue with toluene ($2 \times 10\text{ mL}$). The toluene extract was filtered through a short column of neutral Al_2O_3 . The carbenium salts were isolated by dissolving the toluene-insoluble fraction in water (5 mL). The remaining orange solution was decanted or filtered from the brown, insoluble impurities, and extracted with toluene (5 mL portions) until the organic phase remained colorless. The carbenium thiocyanates were obtained by slow evaporation of the aqueous phase in the form of large colorless crystals.

References: M.K. Denk, S. Gupta, J. Brownie, S. Tajammul, A.J. Lough, *Chem. Eur. J.*, **7**, 4477 (2001).

Type of reaction: C–S bond formation

Reaction condition: solid-state

Keywords: thioureideo-acetamide, phenacyl bromide, cascade reaction, cyclization, solid-solid reaction, heterocycle



Experimental procedures:

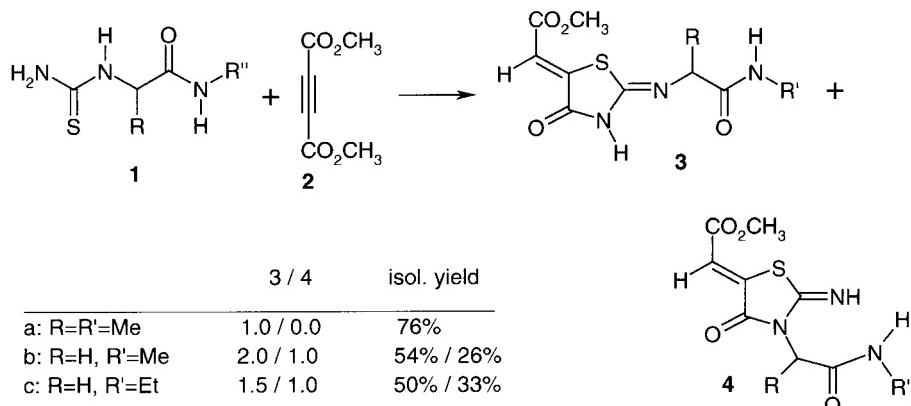
The solid thioureido-acetamide **1a–c** (2.00 mmol) and solid phenacyl bromide **2** (398 mg, 2.00 mmol) were ball-milled in a Retsch MM 2000 mill with a 10-mL beaker (two balls out of stainless steel) at room temperature for 30 min. After drying at 0.01 bar at 80 °C quantitative yields of the pure (hydro)bromides **3a–c** were obtained in all cases. The salts were washed with 5% Na₂CO₃ solution to afford the free bases **4a–c** in pure form in 98, 99 and 98% yield, respectively.

References: J. Schmeyers, G. Kaupp, *Tetrahedron*, **58**, 7241 (2002).

Type of reaction: C–S bond formation

Reaction condition: solid-state

Keywords: thioureideo-acetamide, acetylene dicarboxylate, cascade reaction, ring closure, heterocycle

**Experimental procedures:**

The thioureido-acetamide **1b** (2.00 mmol) and **2** (2.00 mmol) were weighed into a 10-mL ball-mill vessel. The mixture became immediately solid and was ball-milled at 25 Hz for 1 h. **3b** remained insoluble in hot ethyl acetate whereas **4b** dissolved and was separated by filtration. **3b** was recrystallized from DMSO (**3b**, yield 54%). The ethyl acetate extract was evaporated to dryness and the crude solid recrystallized from ethanol (**4b**, yield 26%).

In ethanol solution the **3b**:**4b**-ratio was found to be 0.43:1.0.

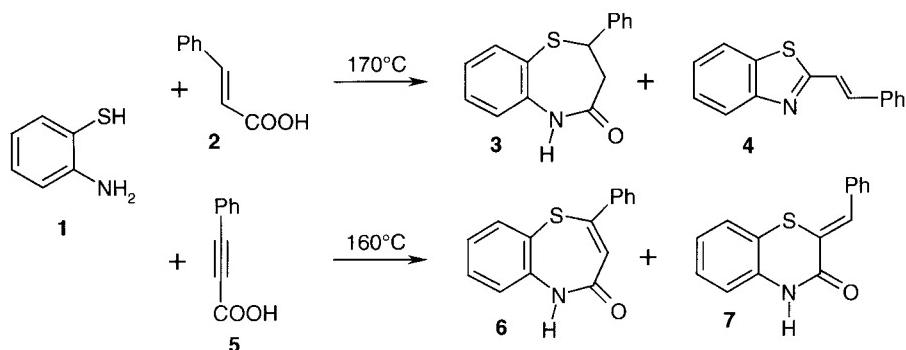
The compounds **3a** and **3c**, **4c** were similarly obtained.

References: J. Schmeyers, G. Kaupp, *Tetrahedron*, **58**, 7241 (2002).

Type of reaction: C–S bond formation

Reaction condition: solvent-free

Keywords: 2-aminothiophenol, cinnamic acid, phenylpropynoic acid, condensation, cyclization, benzothiazepinone, benzothiazole

**Experimental procedures:**

2-Aminothiophenol **1** (8.0 g, 64 mmol) and trans-cinnamic acid **2** (10.0 g, 67.5 mmol) were heated to 170 °C under argon for 2 h. 7.9 g (48%) of **3** crystallized from ethanol. The mother liquor contained **1**, **2**, **3** and **4**. The latter (900 mg, 6%) was isolated by column chromatography on SiO₂ with dichloromethane.

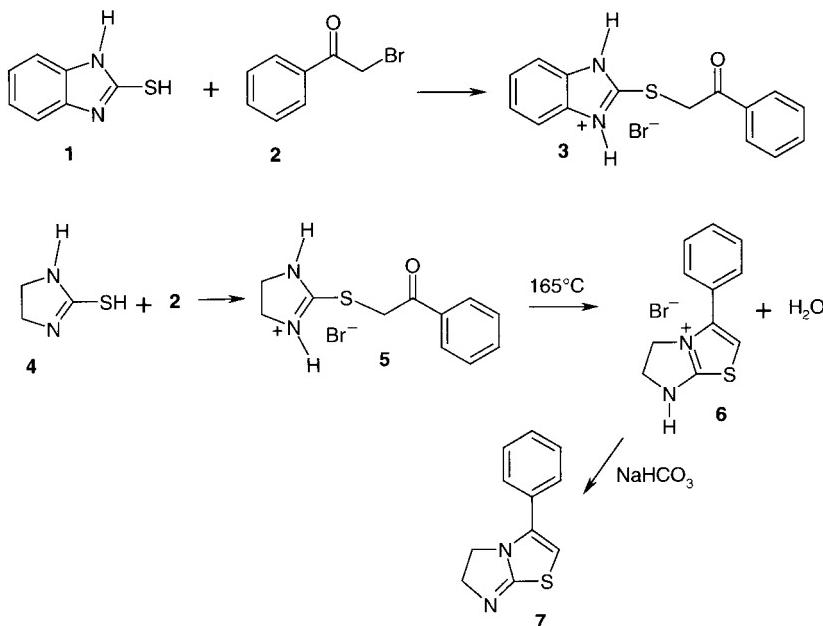
The analogous reaction of **1** (21.7 g, 0.17 mol) and **5** (25 g, 0.17 mol) at 160 °C for 1 h gave a mixture that was cooled to 100 °C and added to 80 mL of boiling acetonitrile. The first crop of yellow crystals (3.4 g) contained **6** and **7** in a 1 : 1-ratio. The cooled mother liquor separated 7.0 g (16%) **6**. The chromatographic separation of **6** and **7** was inefficient.

References: G. Kaupp, E. Gründken, D. Matthies, *Chem. Ber.*, **119**, 3109 (1986).

Type of reaction: C–S bond formation

Reaction condition: solid-state

Keywords: mercaptobenzimidazol, imidazoline-2-thiol, phenacylbromide, thiuronium salt, waste-free, solid-solid reaction

**Experimental procedures:**

Solid 2-mercaptopbenzimidazole **1** (300 mg, 2.00 mmol) or imidazoline-2-thiol **4** (204 mg, 2.00 mmol) and phenacyl bromide **2** (398 mg, 2.00 mmol) were ball-milled at room temperature for 1 h. The yield of pure product **3** or **5** was 100%.

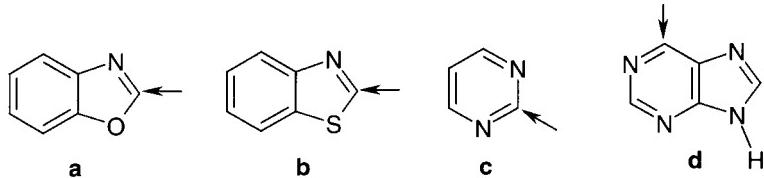
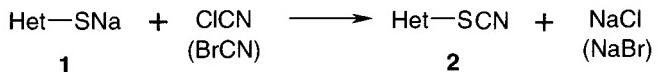
The salt **5** (301 mg, 1.00 mmol) was heated to 165°C for 60 min. After evaporation, the pure bicyclic thiazoliumbromide **6** (280 mg, 100%) was obtained. The free base **7** may be obtained from **6** by extraction from NaHCO₃ solution with CH₂Cl₂. Mp 112–113°C.

References: G. Kaupp, J. Schmeyers, J. Boy, *J. Prakt. Chem.*, **342**, 269 (2000).

Type of reaction: C–S bond formation

Reaction condition: solid-state

Keywords: thiolate, cyanogen chloride, cyanogen bromide, gas-solid reaction, thiocyanate



Experimental procedures:

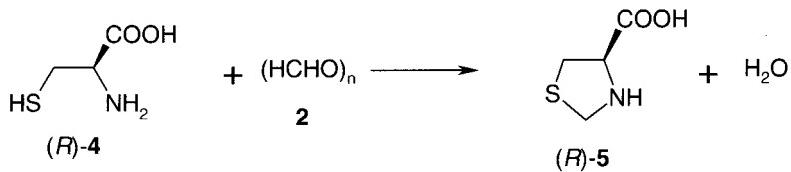
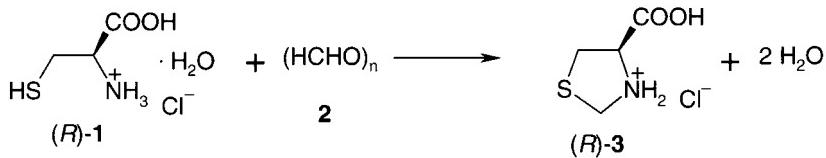
Solid sodium thiolate **1a-d** (10 mmol) was treated with ClCN (1 bar, 11.2 mmol) or with BrCN (1.17 g, 11.0 mmol from a remote flask at a vacuum line) and left overnight. Excess gas was recovered in a cold trap at -196 °C. NaCl (NaBr) was washed away with water and the quantitatively obtained thiocyanates **2a-d** were dried in a vacuum.

References: G. Kaupp, J. Schmeyers, J. Boy, *Chem. Eur. J.*, **4**, 2467 (1998).

Type of reaction: C–S bond formation

Reaction condition: solid-state

Keywords: cysteine, paraformaldehyde, cyclization, waste-free, solid-solid reaction, thiazolidine



Experimental procedures:

(*R*)-**3**: Solid L-cysteine hydrochloride monohydrate (*R*)-**1** (351 mg, 2.00 mmol) and paraformaldehyde (**2**) (60 mg, 2.00 mmol) were ball-milled at room temperature for 1 h. After drying at 0.01 bar at 80 °C, pure (*R*)-**3** (338 mg, 100%) was obtained. (Ref. 1)

(*R*)-**5**: Solid L-cysteine **4** (242 mg, 2.00 mmol) and paraformaldehyde (62 mg of 97% purity, 2.00 mmol) were ball-milled at room temperature for 1 h. After drying at 0.01 bar at 80 °C, pure (*R*)-**5** (263 mg, 100%) was obtained. Mp 196 °C. (Ref. 2)

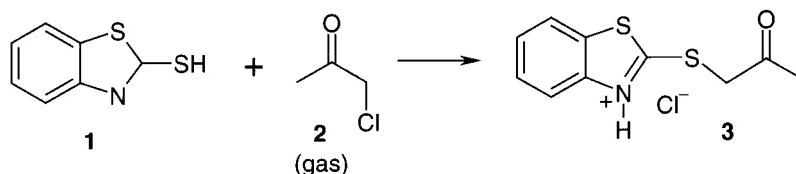
References:

- (1) G. Kaupp, J. Schmeyers, J. Boy, *J. Prakt. Chem.*, **342**, 269 (2000).
 (2) G. Kaupp, J. Schmeyers, J. Boy, *Tetrahedron*, **56**, 6899 (2000).
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Type of reaction: C–S bond formation

Reaction condition: solid-state

Keywords: mercaptobenzothiazole, chloroacetone, gas-solid reaction, thiuronium salt

**Experimental procedure:**

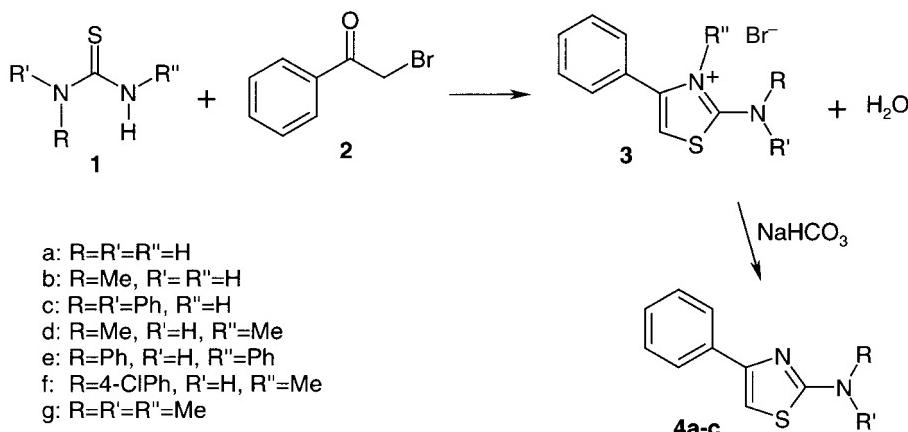
Solid 2-mercaptobenzothiazole **1** (334 mg, 2.00 mmol) in an evacuated 100-mL flask was connected at a vacuum line to a 100-mL flask that contained chloroacetone **2** (500 mg, 5.4 mmol). The whole setup was heated to 60 °C and left for 12 h. Excess gas was removed by evaporation. 520 mg (100%) of pure **3** were obtained.

References: G. Kaupp, J. Schmeyers, J. Boy, *J. Prakt. Chem.*, **342**, 269 (2000).

Type of reaction: C–S bond formation

Reaction condition: solid-state

Keywords: thiourea, bromoacetophenone, cyclization, waste-free, solid-solid reaction, 2-aminothiazole

**Experimental procedures:**

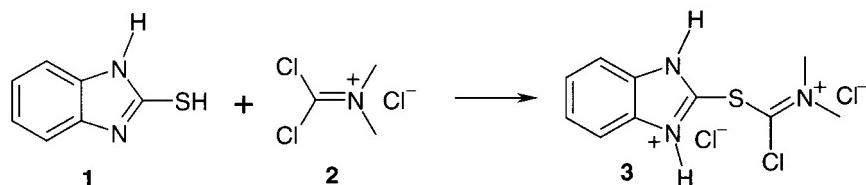
The solid thiourea **1** (2.00 mmol) and phenacyl bromide **2** (398 mg, 2.00 mmol) were ball-milled at room temperature for 30 min. After drying at 0.01 bar at 80 °C quantitative yields of the pure products **3** were obtained in all cases. The free bases **4a-c** can be obtained by trituration with NaHCO₃ solution.

References: G. Kaupp, J. Schmeyers, J. Boy, *J. Prakt. Chem.*, **342**, 269 (2000).

Type of reaction: C–S bond formation

Reaction condition: solid-state

Keywords: Viehe salt, benzimidazole thiol, waste-free, solid-solid reaction

**Experimental procedure:**

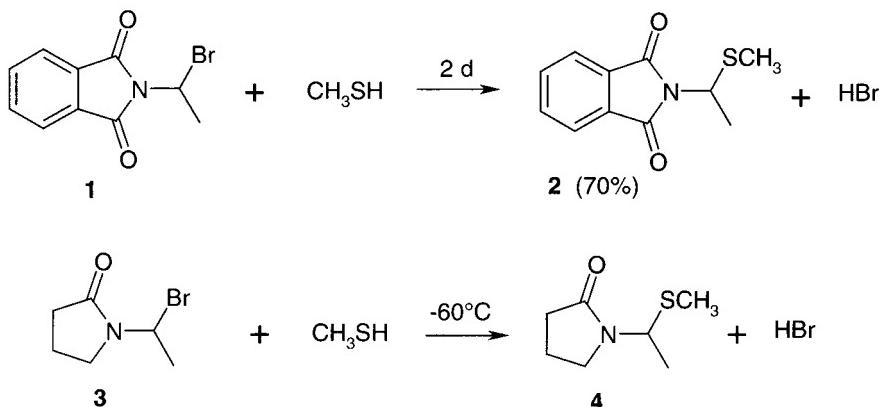
Solid 2-mercaptopbenzimidazole **1** (750 mg, 5.00 mmol) and Viehe salt **2** (815 mg, 5.00 mmol) were ball-milled for 1 h. The yield of pure salt **3** was 1.515 g (100%).

References: G. Kaupp, J. Boy, J. Schmeyers, *J. Prakt. Chem.*, **340**, 346 (1998).

Type of reaction: C–S bond formation

Reaction condition: solid-state

Keywords: methanethiol, *N,S*-acetal, substitution, gas-solid reaction



Experimental procedures:

2: Freshly prepared **1** (from *N*-vinylphthalimide and HBr gas) (1.0 g, 3.9 mmol) in an evacuated 500-mL flask was exposed to CH_3SH (0.5 bar, 11 mmol) at room temperature for 2 days. The gases were pumped off. The conversion was 70% and the product **2** was isolated by preparative TLC (basic SiO_2 , benzene-ethyl-acetate, 4:1).

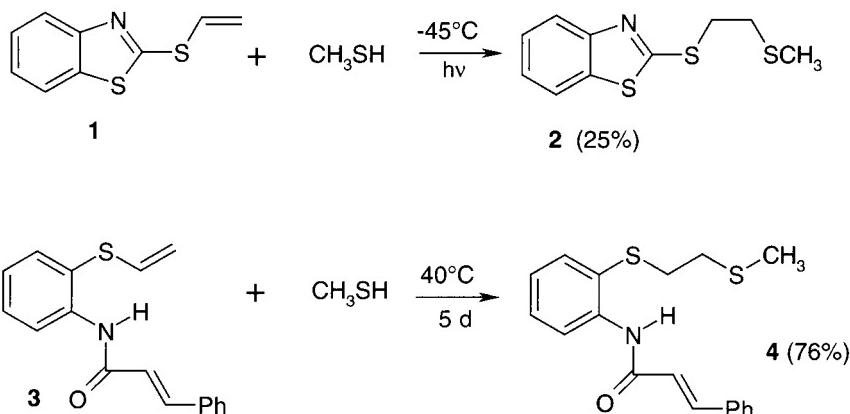
4: *N*-Vinylpyrrolidone (1.00 g, 9.0 mmol) was crystallized on Raschig coils (3 g) at -60°C in an evacuated 500-mL flask. HBr gas (1 bar, 22 mmol) was applied for 2 h. Excess gas was evacuated and the still cooled flask now containing solid **3** was connected at a vacuum line to a 1-L flask that was previously filled with CH_3SH (0.3 bar, 13.4 mmol). After 19 h at -60°C , all gases were evacuated and the crystals which soften above -30°C were chromatographed at basic SiO_2 with ethyl acetate to give oily **4** (600 mg, 42%).

References: G. Kaupp, D. Lübben, O. Sauerland, *Phosphorus, Sulfur, and Silicon*, **53**, 109 (1990).

Type of reaction: C–S bond formation

Reaction condition: solid-state

Keywords: S-vinyl compound, methanethiol, *anti*-Markovnikov addition, gas-solid reaction, thermal, photochemical

**Experimental procedures:**

2: Liquid **1** (0.50 g, 2.6 mmol) was crystallized in an evacuated 500-mL flask at -45°C . Methanethiol at a pressure of 0.3 bar was let in and illumination was performed through the cooling bath out of methanol in a Pyrex vessel using a high-pressure Hg-lamp (Hanau, 150 W) for 5 h. Product **2** was isolated as an oil by preparative TLC. There was no addition in the absence of light.

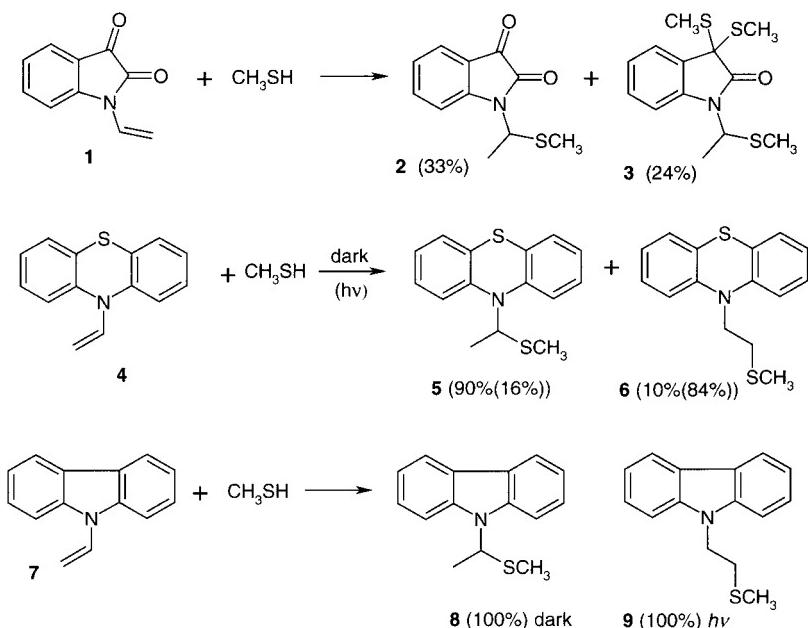
4: Crystalline **3** (200 mg, 0.71 mmol) was exposed to methanethiol (1 bar) in a 250-mL flask at 40°C for 5 days. The solid product **4** was separated from unreacted **3** by preparative TLC (SiO_2 , CH_2Cl_2); mp 106–107 °C.

References: G. Kaupp, D. Lübben, O. Sauerland, *Phosphorus, Sulfur, and Silicon*, **53**, 109 (1990).

Type of reaction: C–S bond formation

Reaction condition: solid-state

Keywords: *N*-vinyl compounds, methanethiol, addition, Markovnikov, *anti*-Markovnikov, gas-solid reaction, thermal, photochemical



Experimental procedures:

Crystalline *N*-vinylization **1** (200 mg, 1.16 mmol) was exposed to 10 mmol methanethiol gas (0.9 bar) at a vacuum line for 21 h. The products **2** and **3** were isolated by preparative TLC on SiO₂ with methylene chloride.

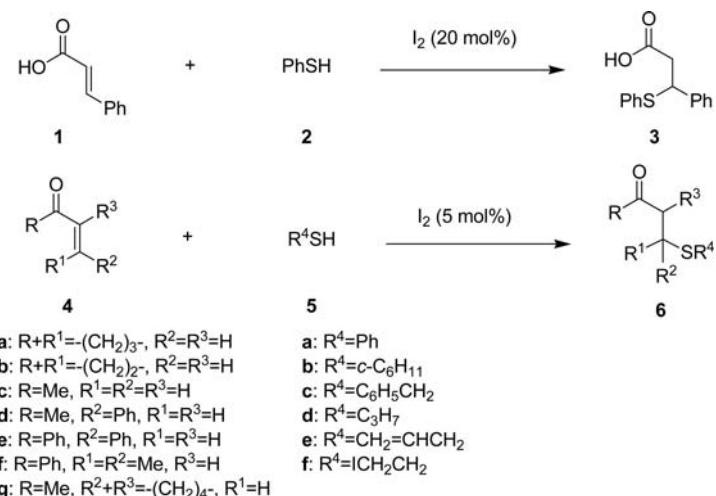
Crystalline *N*-vinylphenothiazine **4** or *N*-vinylcarbazole **7** reacted correspondingly at room temperature for 2 d or 18 h in the dark. Irradiations were performed with a 500-W tungsten lamp in a 250-mL round-bottomed flask under 0.9 bar CH₃SH (**4**: 1.8 mmol, 11 h, rt; **7**: 5.2 mmol, 2 h, 0 °C). The purity of the products was determined by ¹H NMR spectroscopy.

References: G. Kaupp, D. Matthies, *Chem. Ber.*, **120**, 1897 (1987); G. Kaupp, D. Lübben, O. Sauerland, *Phosphorus, Sulfur, and Silicon*, **53**, 109 (1990).

Type of reaction: C–S bond formation

Reaction condition: solvent-free

Keywords: Michael addition, mercaptan, *a*,*β*-unsaturated ketone



Experimental procedures:

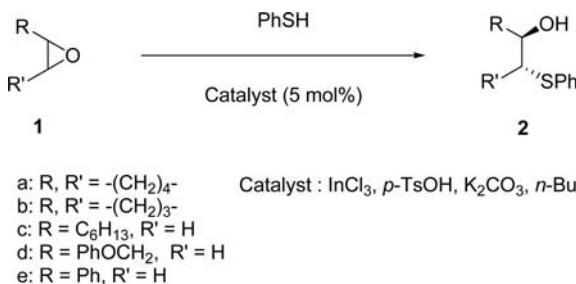
Cyclohexanone **4a** (0.198 g, 2 mmol) and thiophenol **5a** (0.249 g, 2.2 mmol) were mixed together and I_2 (0.025 g, 0.1 mmol) was added and stirred at 0°C for 3 min (monitored through TLC). After adding ice cold saturated sodium thiosulfate solution to the reaction mixture (to remove the traces of iodine), the solution was extracted with dichloromethane (2×5 mL). The combined organic layers were dried over magnesium sulfate, and the crude product passed through a small plug of silica to obtain the pure product **6aa** as a colorless oil (0.40 g, 97%).

References: S. Gao, T. Tzeng, M.N.V. Sastry, C.-M. Chu, J.-T. Liu, C. Lin, C.-F. Yao, *Tetrahedron Lett.*, **47**, 1889 (2006); C.-M. Chu, S. Gao, M.N.V. Sastry, C.-F. Yao, *Tetrahedron Lett.*, **46**, 4971 (2005).

Type of reaction: C–S bond formation

Reaction condition: solvent-free

Keywords: 1,2-epoxide, β -hydroxy sulfide



Experimental procedures:

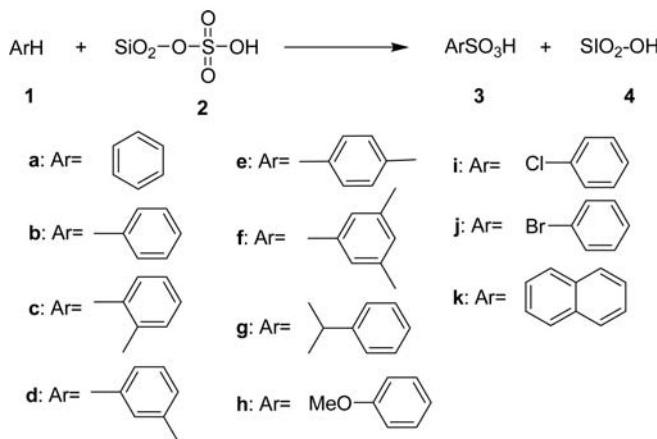
In an oven-dried screw-capped vial thiophenol (1.05 mmol, 0.18 mL) was stirred with the catalyst (5 mol%) for 10 min at 30 °C and then 1,2-epoxide (1.0 mmol) was added. After the times reported, the reaction mixture with InCl₃, K₂CO₃ and *p*-TsOH was treated with diethyl ether, the organic phase was washed with water to remove the catalyst and was worked-up as usual. n-Bu₃P was removed directly by recrystallization in the case of solid products, or by filtration through silica gel in the case of oily products.

References: F. Fringuelli, F. Pizzo, S. Tortoisioli, L. Vaccaro, *Tetrahedron Lett.*, **44**, 6785 (2003).

Type of reaction: C–S bond formation

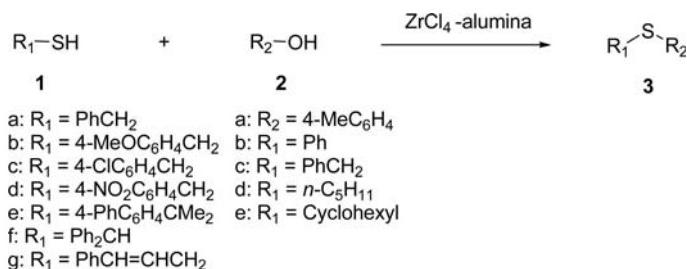
Reaction condition: solvent-free

Keywords: sulfonation, silica sulfuric acid

**Experimental procedures:**

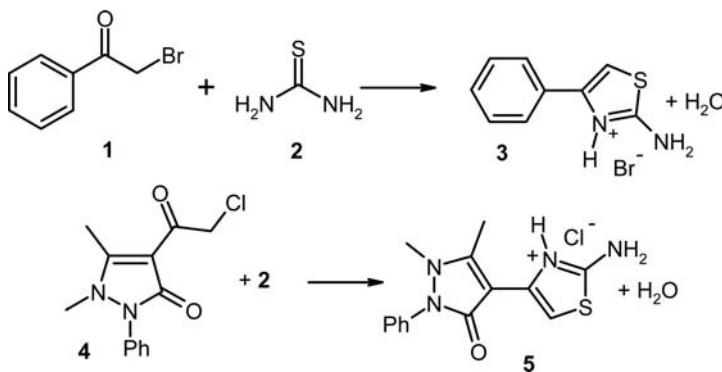
A 25-mL round-bottomed flask was charged with silica sulfuric acid (1.9 g, 5 mmol) and mesitylene (5 mL) and a magnetic stirrer. The reaction mixture was stirred at 80 °C for 30 min, the heterogeneous mixture was then filtered, washed with 10 mL of dichloromethane, and the solvent was removed under reduced pressure. The residue was washed with n-hexane (2×10 mL) and dried in air to produce a white solid (0.75 g, 75% yield), mp: 74–76 °C.

References: A.R. Hajipour, B.B.F. Mirjalili, A. Zarei, L. Khazdooz, A.E. Ruoho, *Tetrahedron Lett.*, **45**, 6607 (2004).

Type of reaction: C–S bond formation**Reaction condition:** solvent-free**Keywords:** S-alkylation, thiol, silica gel**Experimental procedures:**

To a mixture of ZrCl₄ (0.116 g, 0.5 mmol) and dry silica gel [0.3 g (60, 70–230 mesh) dried at 100 °C under vacuum for 24 h] at 50 °C, thiol (1.1 mmol) was added and the mixture was stirred for a few minutes. Then, the alcohol (1 mmol) was added and the mixture was stirred at 50 °C for the appropriate reaction time (monitored by TLC and GC). The reaction mixture was then washed with an aqueous solution of NaOH (10%, 10 mL) and extracted with Et₂O (2×10 mL). The organic layer was separated and dried over anhydrous CaCl₂ and filtered. Evaporation of the solvent afforded the desired product. Further purification was achieved by preparative plate silica chromatography eluting with n-hexane.

References: H. Firouzabadi, N. Iranpoor, M. Jafarpour, *Tetrahedron Lett.*, **47**, 93 (2006).

Type of reaction: C–S bond formation**Reaction condition:** solid-state**Keywords:** large scale, phenylacyl bromide, thiourea, aminothiazole, quantitative, solid-solid reaction, cascade reaction, ball milling, chloroacetyl-antipyrine

Experimental procedure:

200 g quantities of a stoichiometric 1:1-mixture of loosely premixed crystals of **1** and **2**, both of >99% purity, were fed to a stellite 2-L horizontal rotary ball mill (Simoloyer®) with 2 kg steel balls (100Cr6; 5 mm diameter) at 1000 min⁻¹ with water cooling at 15–20 °C for 1 h. The quantitatively formed **3** was milled out for 10 min at 600 min⁻¹ leaving some hold-up, but a quantitative recovery was obtained from the second batch and so on. For quantitative recovery of the last batch an internal air cycle for deposition through a cyclone was used. Semicontinuous production is possible. The free 2-amino-4-phenyl-thiazole could be obtained by neutralization with NaOH in aqueous suspension [1].

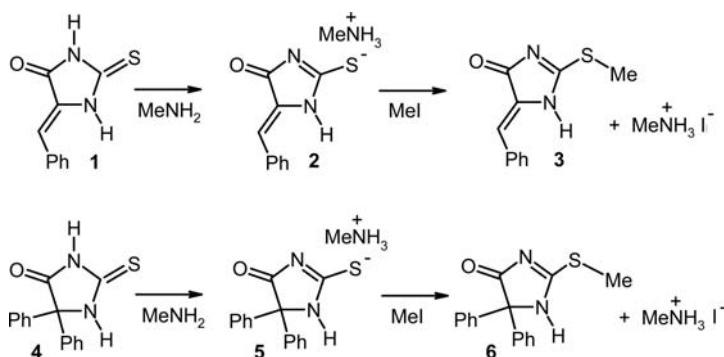
A mixture of 4-(chloroacetyl)-antipyrine **4** (529 mg, 2.00 mmol) and thiourea **2** (152 mg, 2.00 mmol) was ball-milled at 70 °C for 1 h. After drying at 80 °C at 0.01 bar a quantitative yield of the dry salt **5** (645 mg, 100%) was obtained [2].

References: 1. G. Kaupp, *CrystEngComm*, **8**, 794 (2006); small scale: G. Kaupp, J. Schmeyers, J. Boy, *J. Prakt. Chem.*, **342**, 269 (2000); review on synthetic use of **3**: M.A. Metwally, E. Abdel-latif, F.A. Amer, G. Kaupp, *J. Sulfur Chem.*, **25**, 63 (2004); 2. G. Kaupp, F.A. Amer, M.A. Metwally, E. Abdel-latif, *J. Herocycl. Chem.*, **40**, 963 (2003).

Type of reaction: C–S bond formation

Reaction condition: solid-state

Keywords: gas-solid reaction, thiohydantoins, methylamine, methylammonium salts, iodomethane, alkylation

**Experimental procedure:**

5-Benzylidene- or 5,5-diphenyl-thiohydantoin **1** (500 mg, 2.45 mmol) or **4** (500 mg, 1.88 mmol) in a 250-mL flask was exposed to methylamine gas (1 bar) for 1 h at room temperature to give the methylammonium salt **2** or **5**. After collection of the excess gas in a trap at 77 K for recovery, the evacuated flask was connected to an evacuated 250-mL flask containing iodomethane (710 mg,

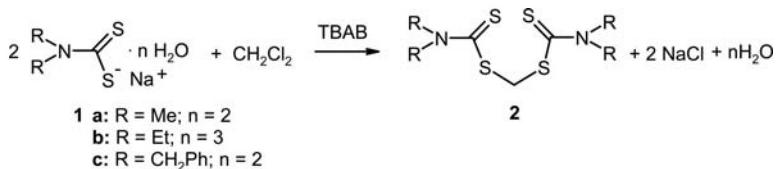
5.0 mmol) at a vacuum line and left at room temperature overnight (initial pressure 0.22 bar). Excess CH₃I vapor was recovered from a cold trap at 77 K for further use. The residue was washed with water and dried to obtain **3** (mp 200 °C) or **6** (mp 212 °C) in quantitative yields.

References: G. Kaupp, *Top. Curr. Chem.*, **254**, 95 (2005).

Type of reaction: C–S bond formation

Reaction condition: solid-state

Keywords: gas-solid reaction, catalysis, dialkyldithiocarbamates, methylene-bis-dithiocarbamates, dithioacetal, dichloromethane, alkylation



Experimental procedure:

The *N,N*-dialkyldithiocarbamate **1** (20 mmol) was well mixed with tetrabutylammonium bromide TBAB (64 mg, 0.2 mmol) in an evacuated 100-mL flask at 30 °C. It was connected to an evacuated 50-mL flask at 20 °C containing dichloromethane (935 mg, 11 mmol). The dichloromethane evaporated within 90 min. After a rest overnight complete conversion to **2** was obtained in all cases. The residual dichloromethane vapor was recovered from a trap at 77 K, washing with water removed NaCl and TBAB, and the product **2** (**a**: mp 153–154 °C; **b**: mp 73–73.5 °C; **c**: mp 130 °C) was dried *in vacuo*.

References: G. Kaupp, *Top. Curr. Chem.*, **254**, 95 (2005).

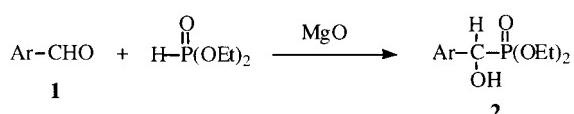
7 Carbon–Phosphorus Bond Formation

7.1 Solvent-Free C=P Bond Formation

Type of reaction: C–P bond formation

Reaction condition: solvent-free

Keywords: diethyl hydrogen phosphite, aromatic aldehyde, magnesia, surface-mediated reaction, diethyl 1-hydroxyvaryl methylphosphonate



- a: Ar=Ph
 - b: Ar=4-MeC₆H₄
 - c: R=4-MeOC₆H₄
 - d: R=3-MeOC₆H₄
 - e: R=3-HOC₆H₄
 - f: R=4-ClC₆H₄
 - g: R=2-ClC₆H₄
 - h: R=4-O₂NC₆H₄

Experimental procedures:

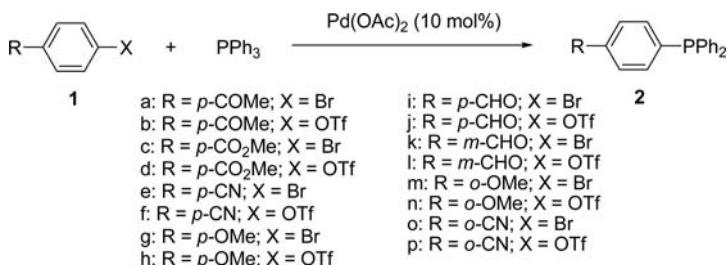
Magnesia (0.8 g, 0.02 mol) was added to a mixture of diethyl hydrogen phosphite (2.76 g, 0.02 mol) and the aldehyde (0.02 mol). This mixture was stirred at room temperature for 2 min–4 h. The solid mixture was washed with CH_2Cl_2 (4×25 mL) and the crude product was isolated in a pure state by simple filtration chromatography through a short plug of silica gel and then was crystallized from CH_2Cl_2 -hexane. For solid aldehydes, prior to addition of magnesia, the mixture of diethyl hydrogen phosphite and the aldehyde must be stirred and heated at 60°C.

References: A. R. Sardarian, B. Kaboudin, *Synth. Commun.*, **27**, 543 (1997).

Type of reaction: C–P bond formation

Reaction condition: solvent-free

Keywords: phosphination, triphenylphosphine, palladium acetate



Experimental procedures:

4-Bromoacetophenone (100 mg, 0.5 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol) and PPh₃ (301 mg, 1.15 mmol) were placed in a Teflon stopcock flask. The flask was then evacuated and refilled with nitrogen three times. The mixture was heated to 115 °C and the reaction was monitored by GC MS or TLC. After completion, the reaction mixture was cooled and the crude product was purified by column chromatography on silica gel using a solvent mixture of hexane–ethyl acetate (20:1) as the eluent to give 4-(diphenylphosphino)acetophenone in 44% yield as a white solid.

References: F. Y. Kwong, C. W. Lai, K. S. Chan, *Tetrahedron Lett.*, **43**, 3537 (2002).

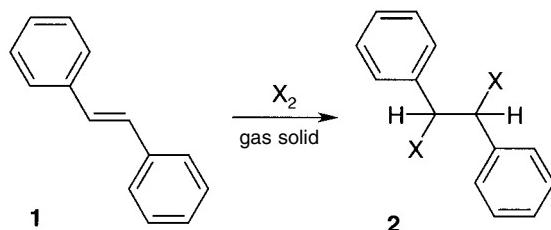
8 Carbon–Halogen Bond Formation

8.1 Solvent-Free C=X Bond Formation

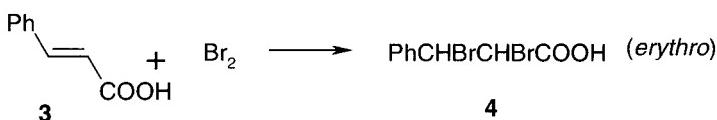
Type of reaction: C-halogen bond formation

Reaction condition: solid-state

Keywords: cinnamic acid, stilbene, halogenation, addition, gas-solid reaction



	<i>meso/dl</i>	yield
a: X=Br pulverized crystals:	62:38	20%
milled crystals:	25:75	100%
b: X=Cl pulverized crystals:	39:61	39%
milled crystals:	18:82	100%



Experimental procedures:

2: 1.00 g (5.6 mmol) of powdered *trans*-stilbene **1** was treated with Cl₂ gas (500 mL, 22 mmol) at room temperature for 6 h. After removing excess Cl₂ gas, the reaction mixture was chromatographed on silica gel (benzene-*n*-hexane, 1:10) to give a 61:39 mixture of *dl*- and *meso*-**2b** (0.55 g, 39%) along with recovered **1** (0.60 g, 60%). The yield of **2b** was increased to 100% and the *cis*-addition strongly enhanced, if the crystals of **1** were ball-milled to μm size prior to a very slow addition of the Cl₂ at 0°C (0.05 bar, 3 h) and then 0.5 bar Cl₂ (24 h).

Similar results were obtained if powdered or ball-milled *trans*-stilbene **1** was treated with the stoichiometric amount of Br₂ gas to give *meso*- and *dl*-**2a**.

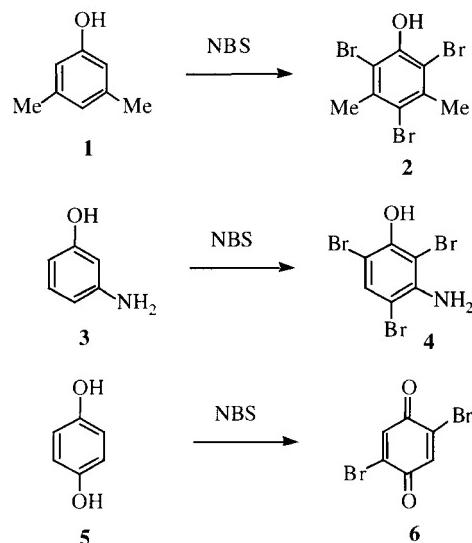
4: Pulverized *trans*-cinnamic acid **3** (2.0 mmol, α or β -modification) and Br₂ gas (5 mmol) gave a 100% yield of the erythro-adduct **4**.

References: G. Kaupp, D. Matthies, *Chem. Ber.*, **120**, 1897 (1987); *Mol. Cryst. Liq. Cryst.*, **161**, 119 (1988); G. Kaupp, *Mol. Cryst. Liq. Cryst.*, **242**, 153 (1994); G. Kaupp, A. Kuse, *Mol. Cryst. Liq. Cryst.*, **313**, 361 (1998).

Type of reaction: C–halogen bond formation

Reaction condition: solid-state

Keywords: phenol, *N*-bromosuccinimide, bromination



Experimental procedures:

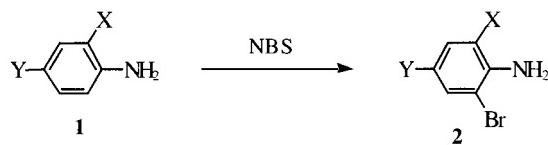
In a typical experiment, the phenol (1 mol) and freshly crystallized NBS (3 mol) were ground in a mortar. The color of the mixture changed immediately from white to yellow-brown. The solid mixture was treated with CCl₄ after an appropriate time (ranging from 1 min to 2 h), the succinimide removed by filtration and the product chromatographed on silica gel (hexane-EtOAc).

References: B. S. Goud, G. R. Desiraju, *J. Chem. Res. (S)*, 244 (1995).

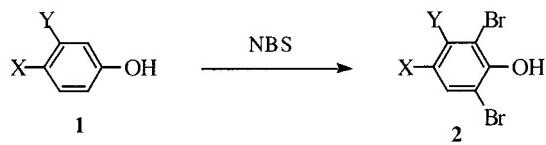
Type of reaction: C–halogen bond formation

Reaction condition: solid-state

Keywords: *N*-bromosuccinimide, aniline, phenol, bromination



- a: X=Me; Y=Br
- b: X=NO₂; Y=OMe
- c: X=Y=Cl



- a: X=COMe; Y=H
- b: X=NO₂; Y=H
- c: X=Cl; Y=Me

Experimental procedures:

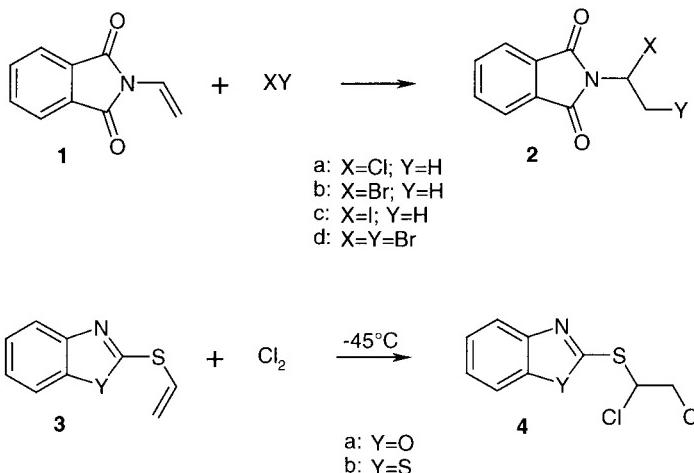
In general the substrate (ca. 1.0 g) and freshly powdered NBS (1:1 molar equivalents) were mixed very gently for a few seconds. After the specified reaction time the mixture was dissolved in petroleum ether and ethyl acetate (10:1) and the mixture was separated using column chromatography. Either grinding of the mixture or monitoring the reaction for a longer time usually resulted in a paste, especially if very low melting reactants or products were involved. The reaction being highly exothermic, reaction temperature and time were varied not only to ensure crystallinity but also to optimize the selectivity and yield. All products were characterized with NMR and mass spectra.

References: J. A. R. P. Sarma, A. Nagaraju, *J. Chem. Soc., Perkin Trans. 2*, 1113 (2000); J. A. R. P. Sarma, A. Nagaraju, K. K. Majumdar, P. M. Samuel, I. Das, S. Roy, A. J. McGhie, *J. Chem. Soc., Perkin Trans. 2*, 1119 (2000).

Type of reaction: C–halogen bond formation

Reaction condition: solid-state

Keywords: *N*-vinyl compounds, *S*-vinyl compounds, halogenation, addition, gas-solid reaction



Experimental procedures:

2: Ground crystals of *N*-vinylphthalimide **1** (100 mg, 0.58 mmol) were exposed to HBr gas (100 mL, 1 bar). The excess gas was evacuated after 30 min and a quantitative yield of **2b** was obtained. HCl and HI reacted similarly to give **2a** and **2c**, while the quantitative addition of Br₂ took 16 h to produce quantitatively **2d**.

The analogous reactions (**a–d**) were obtained with *N*-vinylsaccharin instead of **1** on a gram scale.

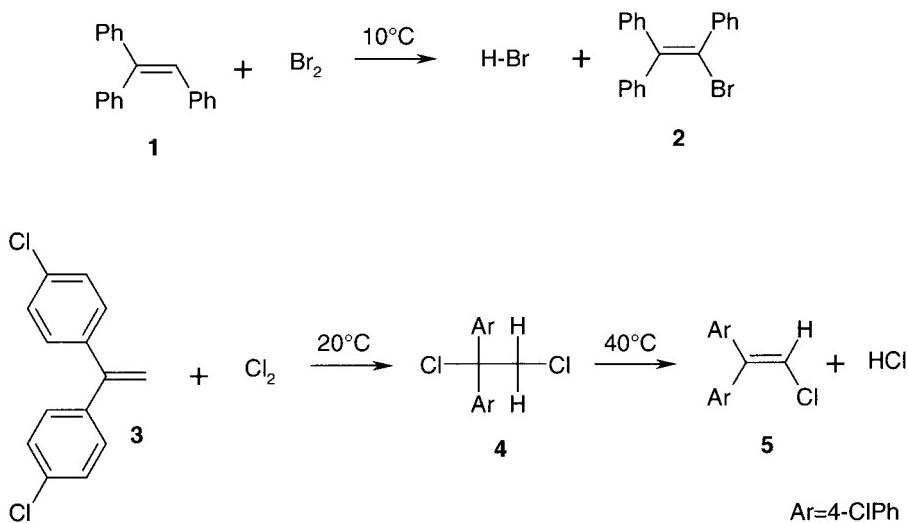
4: The liquid **3a** or **3b** (0.50 g, 2.8 or 2.6 mmol) was spread over Raschig coils (2 g) in a 500-mL flask and it crystallized after evacuation at -45°C. Cl₂ gas (0.5 bar, 11 mmol) was let in. After 5 h, excess gas was evaporated and the yellow solid **4a** or **4b** obtained directly pure with quantitative yield.

References: G. Kaupp, D. Matthies, *Chem. Ber.*, **119**, 2387 (1986); *Mol. Cryst. Liq. Cryst.*, **161**, 119 (1988); G. Kaupp, D. Lübben, O. Sauerland, *Phosphorus, Sulfur, and Silicon*, **53**, 109 (1990).

Type of reaction: C–halogen bond formation

Reaction condition: solid-state

Keywords: 1,1-bisarylethylene, triphenylethylene, halogenation, stilbene, elimination, gas-solid reaction, 1-halogeno-2,2-diarylethene, 1-halogeno-1,2,2-triphenylethene



Experimental procedures:

Powdered triphenylethylene **1** (1.00 g, 3.9 mmol) or 1,1-bis-(4-chlorophenyl)-ethylene **3** (1.37 g, 5.5 mmol) was treated with Br₂ gas (4.24g, 26.5 mmol from a connected flask) or 500 mL Cl₂ gas (1 bar, 22 mmol) at 10°C for 64 h (in the dark) or at 20°C for 3 h. The intermediate 1,2-dihalogeno-1,1-diarylethanes eliminated quantitatively HBr or HCl (**4** at 40°C, 3h) to give a 94% or a 100% yield of the products **2** or **5**. Crystalline **5** was obtained pure, **2** was separated from residual **1** by crystallization from *n*-heptane.

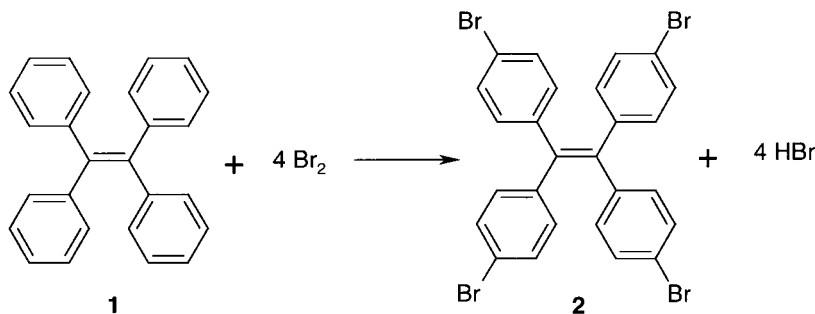
Stirring would certainly have enhanced both the rate of reaction and the yield in the case of **1**.

References: G. Kaupp, D. Matthies, *Chem. Ber.*, **120**, 1897 (1987); *Mol. Cryst. Liq. Cryst.*, **161**, 119 (1988); G. Kaupp, A. Kuse, *Mol. Cryst. Liq. Cryst.*, **313**, 361 (1998).

Type of reaction: C–halogen bond formation

Reaction condition: solid-state

Keywords: tetraphenylethylene, Br₂, substitution, autocatalysis, waste free, gas-solid reaction

**Experimental procedure:**

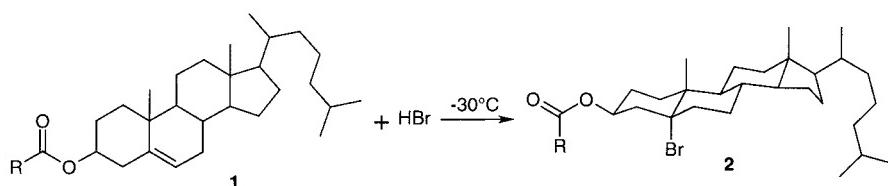
Tetraphenylethylene **1** (1.00 g, 3.0 mmol) was treated with Br_2 (3.2 g, 20 mmol) in a previously evacuated 2-L flask that was rotated around a horizontal axis at room temperature for 12 h. The HBr/Br_2 -mixture was condensed at a vacuum line to a recipient at -196°C from where pure HBr was distilled off during thawing to -78°C under vacuum for further use of the gases. The solid product **2** (1.95 g, 100%) was obtained in pure form.

References: G. Kaupp, A. Kuse, *Mol. Cryst. Liq. Cryst.*, **313**, 361 (1998).

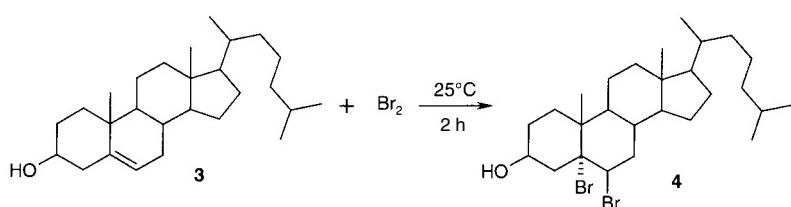
Type of reaction: C–halogen bond formation

Reaction condition: solid-state

Keywords: cholesterol ester, stereospecific halogenation, waste-free, gas-solid reaction



a: R= $(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CH}_3$ (*cis*) (10 h)
b: R= Me (6 days)



Experimental procedures:

Powdered cholesterol oleate **1a** (3.00 g, 4.6 mmol) was evacuated in a 500 mL flask and cooled to -30°C . HBr gas (1 bar, 22 mmol) was let in. After 10 h, excess gas was pumped off and condensed in a cold trap for further use. The quantitatively obtained crystals **2a** were collected in pure form.

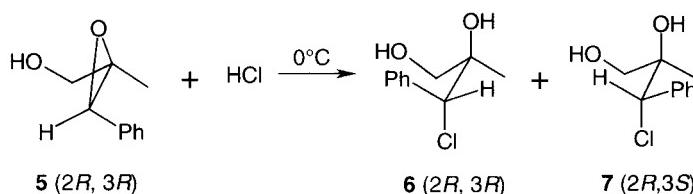
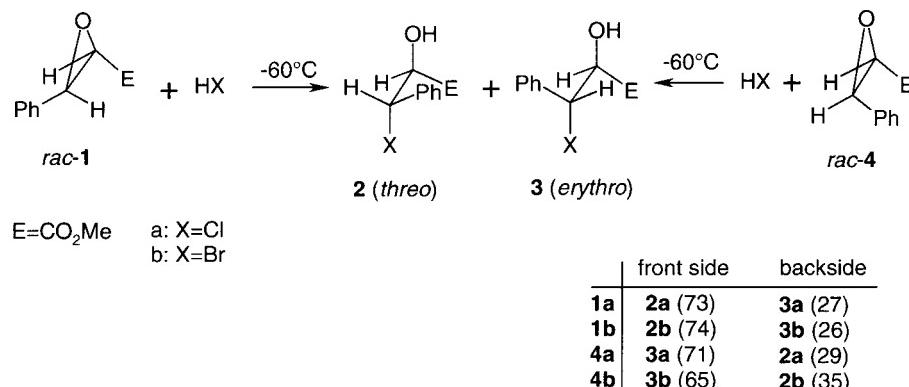
Similarly, quantitative yields of **2b** and **4** were obtained.

References: G. Kaupp, C. Seep, *Angew. Chem.*, **100**, 1568 (1988); *Angew. Chem. Int. Ed. Engl.*, **27**, 1511 (1988).

Type of reaction: C–halogen bond formation

Reaction condition: solid-state

Keywords: epoxide, stereoselective, addition, ring opening, gas-solid reaction

**Experimental procedures:**

Liquid *rac*-**1** (500 mg, 2.8 mmol) was crystallized by cooling to -60°C in a 100-mL flask under vacuum. HCl gas (1 bar, 4.5 mmol) was let in through a vacuum line. After 15 h at -60°C the excess gas was pumped off and 600 mg (100%) yellow crystals (73:27 mixture of **2a** and **3a**) were obtained that melted at room temperature. **2a** (*mp* 65–67 °C) was obtained pure by crystallization from *n*-hexane, though involving heavy losses.

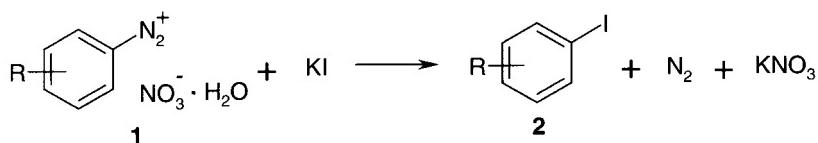
Similarly, the reactions of *rac*-**1** and HBr, or *rac*-**4** and HCl or HBr, or **5** (*2R,3R*) and HCl gave the selectivities as indicated in complete conversions without side-products.

References: G. Kaupp, A. Ulrich, G. Sauer, *J. prakt. Chem.*, **334**, 383 (1992).

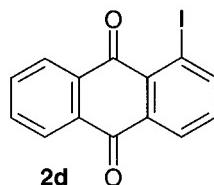
Type of reaction: C–halogen bond formation

Reaction condition: solid-state

Keywords: solid diazonium salt, potassium iodide, iodination, solid-solid reaction, aryl iodide



- a: R= 4-NO₃
- b: R= 4-COOH
- c: R= 4-Br
- d: R= 2,3-(CO-C₆H₄-CO)
- e: R= 4-CN
- f: R= 2-COOH



Experimental procedures:

Caution: Solid diazonium salts are heat- and shock-sensitive; do not ball-mill!

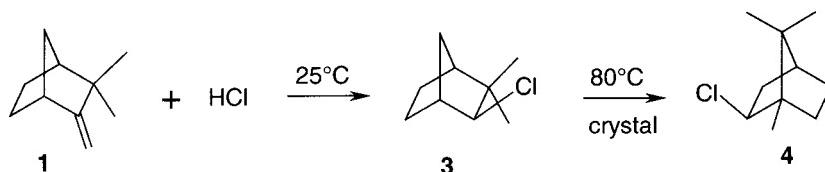
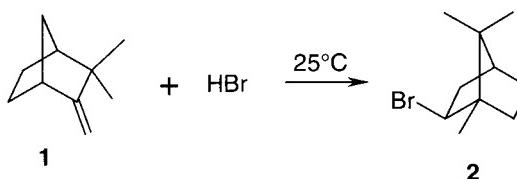
Potassium iodide (830 mg, 5.0 mmol) was finely ground in an agate mortar and the diazonium salt **1** (0.50 mmol) added in five portions and co-ground for 5 min, each. After a 24 h rest with occasional grinding, the diazonium band in the IR spectra had completely disappeared. The potassium salts were removed by washings with cold water. The yield of pure aryl iodide **2** was 100% throughout.

References: G. Kaupp, A. Herrmann, J. Schmeyers, *Chem. Eur. J.*, **8**, 1395 (2002).

Type of reaction: C–halogen bond formation

Reaction condition: solid-state

Keywords: camphene, rearrangement, stereospecific, waste-free, gas-solid reaction, isobornyl halide



Experimental procedures:

2: Camphene 1 (mp 51–52 °C; 1.09 g, 8.0 mmol) was treated with HBr gas (0.5 bar, 11.2 mmol) at 25 °C for 10 h in an evacuated 50-mL flask that was connected to a 500-mL flask. Excess gas was recovered in a cold trap at –196 °C. The solid iso-bornylbromide 2 was quantitatively obtained.

3: Camphene 1 (1.09 g, 8.0 mmol) was treated with HCl gas (0.5 bar, 11.2 mmol) at 25 °C for 10 h in an evacuated 50-mL flask that was connected to a 500-mL flask. Excess gas was recovered in a cold trap at –196 °C. The pure solid camphene hydrochloride 3 was quantitatively obtained.

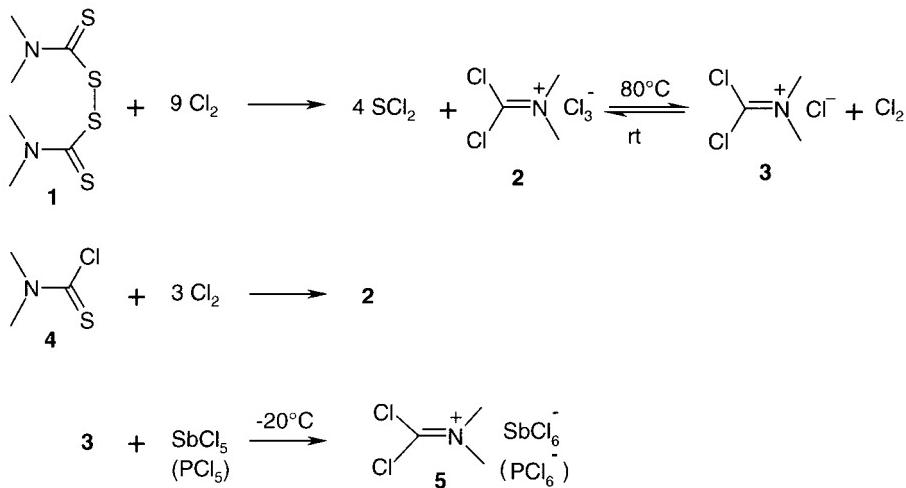
4: The Wagner Meerwein rearrangement of 3 to 4 occurred rapidly in solution but slowly in the crystal where it was complete after three years at room temperature or in 6 h at 80 °C.

References: G. Kaupp, J. Schmeyers, J. Boy, *Chemosphere*, **43**, 55 (2001).

Type of reaction: C–halogen bond formation

Reaction condition: solid-state

Keywords: dimethylthiocarbamoyl compounds, chlorination, gas-solid reaction, solid-solid reaction, Viehe salt



Experimental procedures:

3: Tetramethylthiocarbamoyl disulfide **1** (1.20 g, 5.00 mmol) or dimethyl-thiocarbamoylchloride **4** (1.24 g, 10.0 mmol) were reacted in an evacuated 1-L flask with Cl₂ (1 bar, 45 mmol). After 10 h, all Cl₂ was consumed to form solid **2** with included SCl₂. This product was heated to 80 °C for 2 h in a vacuum with a cold trap (-196 °C) condensing the liberated Cl₂ and SCl₂. The yield of pure **3** was 1.62 g (100%) in both cases.

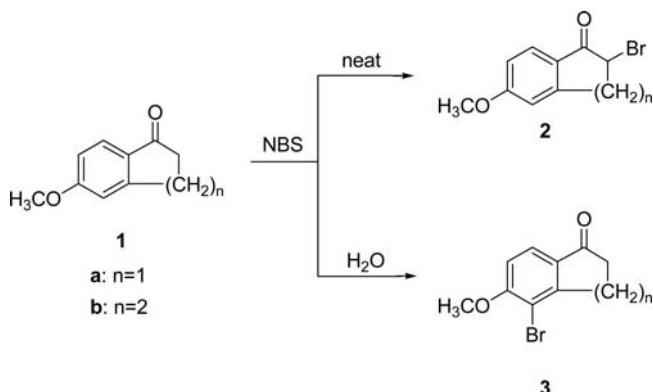
5: Solid SbCl₅ (598 mg, 2.00 mmol) or PCl₅ (417 mg, 2.00 mmol) was weighed to a 10-mL steel beaker of a ball-mill under N₂ and the balls were added. The beaker was closed and cooled to -20 °C prior to the addition of Viehe salt **3** (325 mg, 2.00 mmol) that was previously cooled to -20 °C under N₂. The closed beaker was connected to the cooling system (-20 °C) and milling was performed at -20 °C for 1 h. The highly reactive **5** was quantitatively obtained and should be handled under protecting gas throughout.

References: G. Kaupp, J. Boy, J. Schmeyers, *J. Prakt. Chem.*, **340**, 346 (1998).

Type of reaction: C–halogen bond formation

Reaction condition: solvent-free

Keywords: NBS, bromination, ketone

**Experimental procedures:**

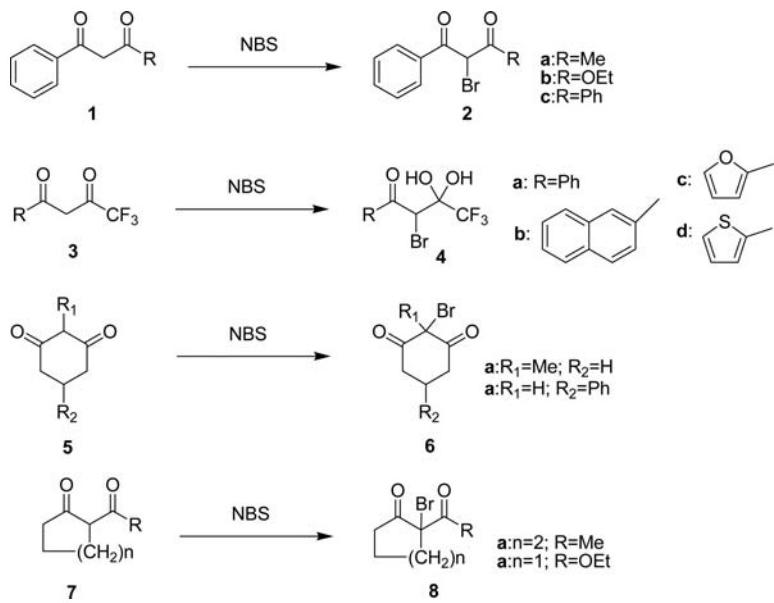
Ketone **1a** (1 mmol), *N*-bromosuccinimide (NBS, 1 mmol) and *p*-toluenesulfonic acid (PTSA, 0.1 mmol) were ground in a porcelain mortar and then heated to 60 °C for 10 min. This turned the reaction mixture into a paste. When the reaction mixture was cooled to room temperature, isolation using *tert*-butyl methyl ether–water extraction gave a crude product containing **2a** (87%), which was additionally purified by crystallization from ethanol. Dibromination was achieved using a similar procedure with 2 mmol of NBS by heating at 80 °C for 1 h. The crude product contained 2,2-dibromo-5-methoxyindanone (99%), which was crystallized from ethanol to give the pure compound, mp 109–110 °C.

References: I. Pravst, M. Zupan, S. Stavber, *Tetrahedron Lett.*, **47**, 4407 (2006).

Type of reaction: C–halogen bond formation

Reaction condition: solvent-free

Keywords: bromination, 1,3-diketone, *N*-bromosuccinimide

**Experimental procedures:**

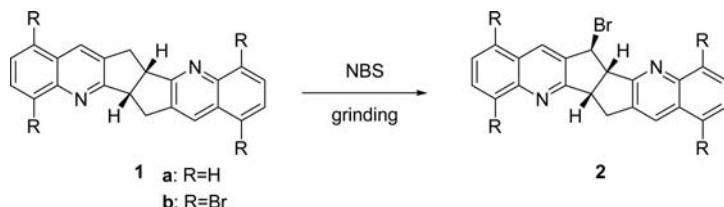
Ketone **1c** (897 mg, 4 mmol) and *N*-bromosuccinimide (NBS, 712 mg, 4 mmol) were triturated together in a porcelain mortar for 5 min and after 1 h water (4 mL) was added and the mixture converted into a paste. After filtration and additional washing with water, the crude product was dried overnight in a desiccator under reduced pressure and yielded 1.187 g (98%) of pure product **2c**.

References: I. Pravst, M. Zupan, S. Stavber, *Green Chem.*, **8**, 1001 (2006).

Type of reaction: C–halogen bond formation

Reaction condition: solid-state

Keywords: *N*-bromosuccinimide, diquinoline

**Experimental procedures:**

5ba,6,12ba,13-tetrahydropentaleno[1,2-*b*:4,5-*b*]diquinoline **1** (60.00 mg, 0.195 mmol) and NBS (120 mg, 0.674 mmol) were placed in a Retsch Mixer Mill

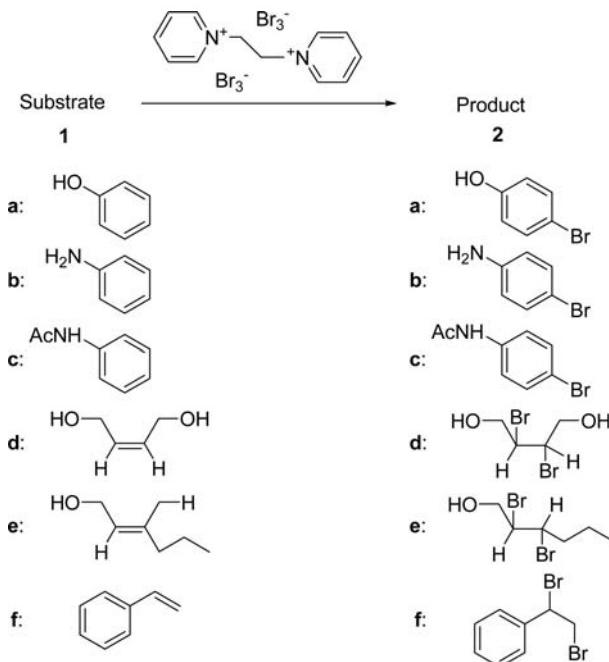
(model MM200) grinding jar and the reaction mixture was ground at a frequency of 15 s^{-1} . The progress of the reaction was monitored at 1 h intervals by using TLC and NMR. Until 4 h of grinding, no reaction was observed. The reaction began in the fifth hour and was complete in the sixth hour. The crude product was then mixed with a small volume of acetone and the soluble material decanted onto a flash chromatography column which was eluted with the same solvent. The solvent was evaporated under reduced pressure to obtain the pure compound **2a** in 85% yield.

References: A. N. M. M. Rahman, R. Bishop, R. Tan, N. Shan, *Green Chem.*, **7**, 207 (2005).

Type of reaction: C–halogen bond formation

Reaction condition: solvent-free

Keywords: 1,2-dipyridiniumditribromide-ethane, bromination



Experimental procedures:

A mixture of acetanilide (**1c**) (0.675 g, 5 mmol) and 1,2-dipyridiniumditribromide-ethane (1.66 g, 2.5 mmol) was ground in a mortar with a pestle at room temperature. After disappearance of the starting material (monitored by TLC by taking a small amount of the mixture and dissolving it in ethyl acetate), the reaction mixture was transferred into a G₃ sintered funnel and washed with water

(5×5 mL), and the solid was dried to yield 1021 mg (95%) of *p*-bromoacetanilide (**2c**).

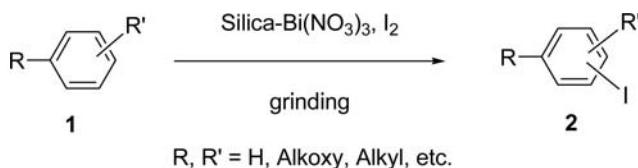
References: V. Kavala, S. Naik, B. K. Patel, *J. Org. Chem.*, **70**, 4267 (2005).

Type of reaction: C–halogen bond formation

Reaction condition: solvent-free

Keywords: bismuth nitrate pentahydrate, iodine, co-grinding

Experimental procedures:



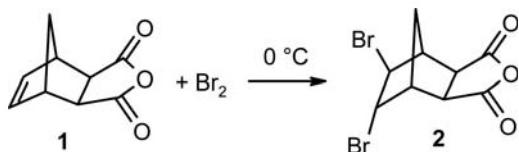
To a pre-weighed sample of silica-gel (2.5 g) was added $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ (1.7 mmol) and iodine (3.0 mmol) which was then co-ground in an agate mortar. To the free flowing powder thus obtained was added the organic substrate (5.0 mmol) and the contents were carefully ground to obtain a fine homogenous powder. This mixture was allowed to stand for the specified time, at room temperature. On completion (TLC or GC analysis) the reaction mixture was desorbed with dichloromethane (3×10 mL). The organic extracts were successively washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution, dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure. The crude product was purified by column chromatography to furnish the pure iodides.

References: V.M. Alexander, A.C. Khandekar, S.D. Samant, *Synlett*, 1895 (2003).

Type of reaction: C–halogen bond formation

Reaction condition: solid-state

Keywords: quantitative, gas-solid reaction, bromine, norborn-5-ene-2*exo*,3*exo*-di-carboxylic acid-anhydride, addition, stereospecific



Experimental procedure:

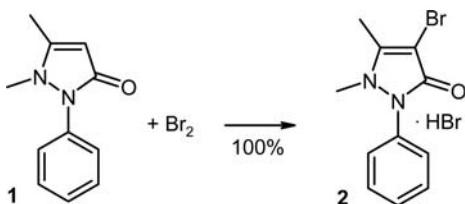
The *exo*-anhydride **1** (328 mg, 2.00 mmol) was placed in a 100-mL flask that was cooled to 0°C and evacuated. An evacuated 250-mL flask containing Br₂ (0.48 g, 3 mmol, 0.27 bar) was connected at a vacuum line and the reacting gas was slowly let in (in four portions) over 1 h so that the pressure in the cooled flask never rose above 0.1 bar. After standing overnight the excess gas was evaporated to a trap at 77 K for recovery, until the crystals **2** (648 mg, 100%) were colorless.

References: G. Kaupp, *Top. Curr. Chem.*, **254**, 95 (2005).

Type of reaction: C–halogen bond formation

Reaction condition: solid-state

Keywords: gas-solid reaction, bromine, antipyrine, substitution, quantitative

**Experimental procedures:**

Antipyrine **1** (376 mg, 2.00 mmol) was placed in a 100-mL flask that was cooled to 0°C and evacuated. An evacuated 250-mL flask containing Br₂ (0.64 g, 4 mmol, 0.36 bar) was connected at a vacuum line and the reacting gas was gradually let in (in four portions over 1 h). After standing overnight colorless crystals of **2** (455 mg, 100%) were obtained. Free 4-bromoantipyrine could be obtained from the salt **2** by aqueous washing.

References: G. Kaupp, Prediction of reactivity in solid-state chemistry, in *Making Crystals by Design* (D. Braga, F. Grepioni eds), Wiley-VCH, Weinheim, **2007**, pp. 87–148.

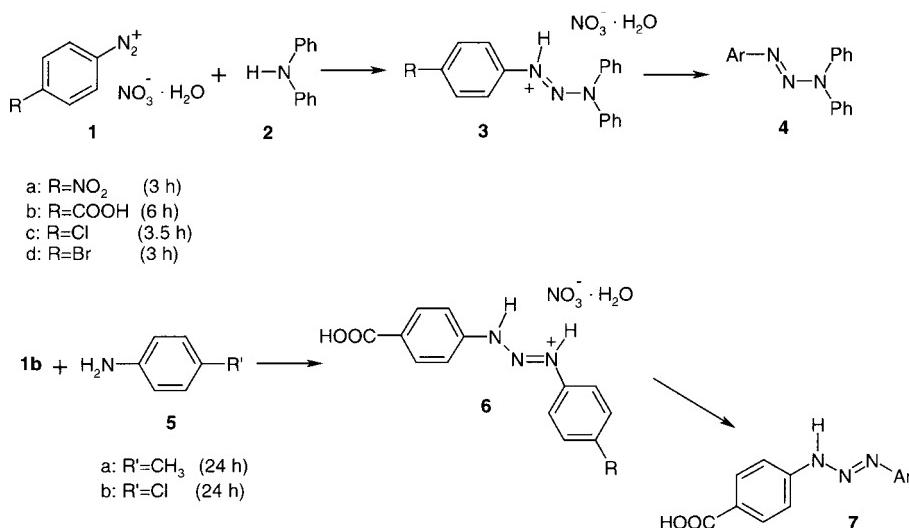
9 Nitrogen–Nitrogen and Nitrogen–Sulfur Bond Formation

9.1 Solvent-Free N–N Bond Formation

Type of reaction: N–N bond formation

Reaction condition: solid-state

Keywords: solid diazonium salt, anilines, diphenylamine, gas-solid reaction, triazenes



Experimental procedures:

Caution: Solid diazonium salts are heat- and shock-sensitive; do not ball-mill solid diazonium salts!

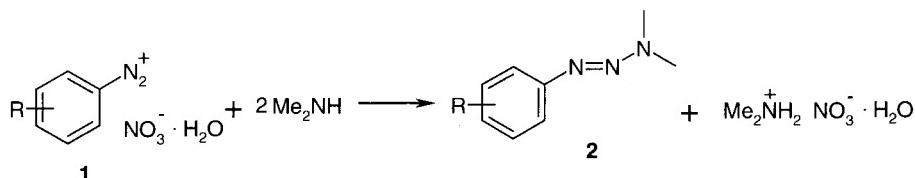
Diphenylamine **2** (1.00 mmol) or substituted aniline **5a,b** (1.00 mmol) was ground in an agate mortar. The diazonium salt **1** (1.00 mmol) was added in five portions and co-ground for 5 min. To complete the reaction, the solid mixture was transferred to a test tube and then exposed to ultrasound in a cleaning bath, the temperature of which was maintained at 20–25 °C for the time given, when all of the diazonium band in the IR had disappeared. The triazenum salts **3** or **6** were obtained quantitatively. The free triazene bases **4** or **7** were obtained by trituration of their salts with 0.1 n NaOH (20 mL), filtering, washing (H₂O) and drying. The yield was >99% in all cases.

References: G. Kaupp, A. Herrmann, J. Schmeyers, *Chem. Eur. J.*, **8**, 1395 (2002).

Type of reaction: N–N bond formation

Reaction condition: solid-state

Keywords: solid diazonium salt, amine, gas-solid reaction, triazene



a: R=4-COOH

b: R=4-Br

c: R=4-Cl

d: R=4-NO₂

e: R=3-NO₂

f: R=2-COOH

g: R=4-CN

h: R=4-SO₃H (as zwitterion)

i: R=2-SO₃H (as zwitterion)

j: R=4-(4-C₆H₄N₂NO₃ · H₂O)

Experimental procedures:

Caution: These reactions may occur violently, use protecting shield!

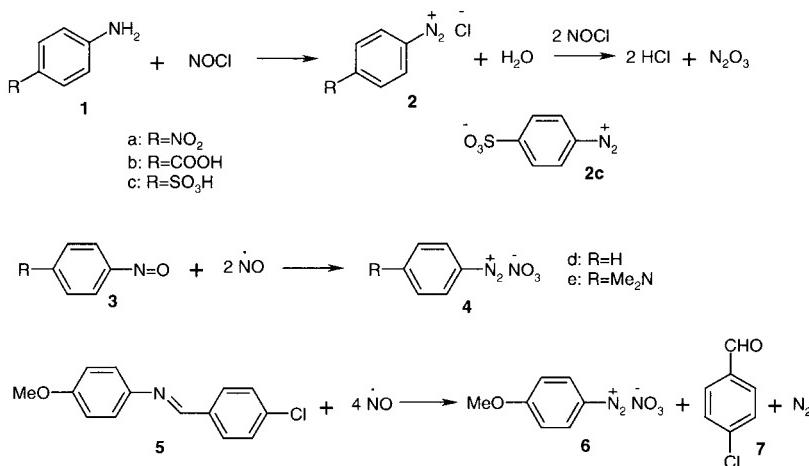
The diazonium nitrate (**1a–g**, 0.70 mmol, **1j**, 0.35 mmol) or the zwitterion (**1h, i**, 0.70 mmol) or 4-nitrophenyldiazonium tetrafluoroborate (**1d·BF4**; 0.70 mmol) in an evacuated 250-mL flask was cautiously treated with dimethylamine (**1a, f, h, i** and **1d·BF4** at room temperature; **1b, c, d, e, g, j** at 0 °C): slow application was obtained by connecting to an evacuated flask with 70 mg (1.56 mmol) Me_2NH cooled to –196 °C and then removing the liquid nitrogen bath, for security reasons behind a protecting shield. After the thawing-up, the slight excess of gas was condensed back to the other flask and quantitative reaction secured by weighing. The triazenes **2** were extracted from the dimethylammonium salts with dry EtOAc and evaporated. The purity was checked with mp and by spectroscopic techniques.

References: G. Kaupp, A. Herrmann, *J. Prakt. Chem.*, **339**, 256 (1997).

Type of reaction: N–N bond formation

Reaction condition: solid-state

Keywords: anilines, nitrosobenzene, azomethine, nitrosyl chloride, nitrogen monoxide, diazotization, gas-solid reaction, solid diazonium salts



Experimental procedures:

Caution: Solid diazonium salts explode upon heating, upon shock and upon grinding at sharp edges!

2: The solid aniline **1** (1.00 mmol) in an evacuated 250-mL flask was connected by a vacuum line to a 250-mL flask that was filled with NOCl (1 bar, 11 mmol). After 24 h, the gases were condensed back into the gas reservoir at -196 °C, absorbed in water and neutralized with NaOH for disposal. The yellow-orange crystals **2** were quantitatively obtained.

4: The nitrosobenzene **3d** or **3e** (2.00 mmol) in an evacuated 250-mL flask was connected by a vacuum line with a 250-mL flask containing NO (1 bar, 11 mmol) that had been freed from traces of NO₂ by storing over 4-chloroaniline. After storing the sample in a refrigerator at 4 °C for 24 h or 48 h, respectively, excess gas was recovered in a cold trap at -196 °C. Pure **4** was quantitatively obtained.

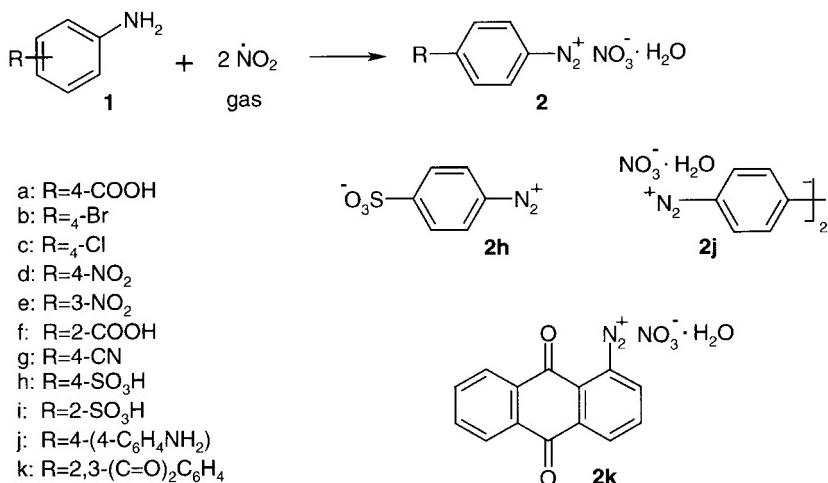
6: The imine **5** (491 mg, 2.00 mmol) in an evacuated 250-mL flask was connected by a vacuum line to a 250-mL flask containing NO (1 bar, 11 mmol) that was freed from traces of NO₂. After 24 h, excess gas was recovered as above and the solid material washed with dry ether (2×10 mL) in order to remove **7** and non-polar impurities. The product **6** (315 mg, 80%) was spectroscopically pure.

References: G. Kaupp, A. Herrmann, J. Schmeyers, *Chem. Eur. J.*, **8**, 1395 (2002).

Type of reaction: N–N bond formation

Reaction condition: solid-state

Keywords: anilines, nitrogen dioxide, diazotization, waste-free, gas-solid reaction, solid diazonium salt



Experimental procedures:

Caution: Solid diazonium salts explode upon heating to the melting point and upon shock or upon grinding at sharp edges. Do not ball-mill!

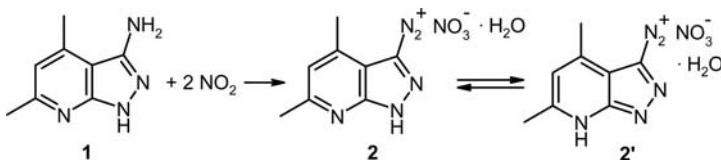
The solid aniline derivatives **1a–k** (2.0 mmol, 1.0 mmol with **1j**) were treated with NO₂ gas in an evacuated 50-mL flask at 0 °C (**1a, k** at room temperature). NO₂ (460 mg, 10 mmol) from a 250-mL flask was applied through a stopcock in 5 small portions, each after the brown color of the previous portion had disappeared. Finally, the excess gas was let in and the reaction completed by 6 h rest. Excess gas was recovered by cooling the 250-mL flask to –196 °C. Quantitative conversion to the diazonium nitrate hydrates **2** (except with **2d** where not all of the water could be accommodated by the crystal: 92%) was secured by weight, spectroscopy and quantitative coupling with β-naphthol. **2h, i** were freed from HNO₃ and water at 5×10^{-4} Torr (12 h) and were obtained as zwitterions. **2d** was purified by washings with ethyl acetate in order to remove unreacted **1d**, a technique that should be applied in all cases where the aniline derivative **1** contained unpolar impurities that are most easily removed at that stage. Thus, the synthesis of **2k** started with **1k** of 97% purity. **2k** was obtained in pure form by two washings with EtOAc.

References: G. Kaupp, A. Herrmann, *J. Prakt. Chem.*, **339**, 256 (1997); G. Kaupp, A. Herrmann, J. Schmeyers, *Chem. Eur. J.*, **8**, 1395 (2002).

Type of reaction: N–N bond formation

Reaction condition: solid-state

Keywords: quantitative, solid diazonium salt, aminopyrazolopyridine, gas-solid ion, diazotization



Experimental procedure:

Caution: Solid diazonium salts explode upon heating, upon shock, and upon grinding at sharp edges!

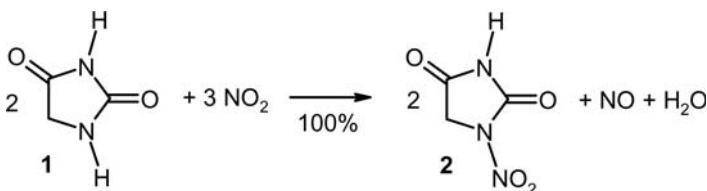
The aminopyrazolopyridine **1** (324 mg, 2.0 mmol) was exposed to NO_2 gas (360 mg, 7.8 mmol) in an evacuated 250-mL flask for 6 h at room temperature with occasional careful shaking. The excess NO_2 was recovered from a trap at 77 K. The diazonium nitrate **2/2'** (508 mg, 100%) exploded at 143 °C when melting. It can be used directly for coupling reactions without removal of the water of reaction.

References: G. Kaupp, M.A. Metwally, F.A. Amer, E. Abdel-latif, *Eur. J. Org. Chem.*, **2003**, 1545.

Type of reaction: N–N bond formation

Reaction condition: solid-state

Keywords: gas-solid reaction, nitration, hydantoin, *N*-nitrohydantoin, nitramine, nitrogen dioxide, nitrogen monoxide



Experimental procedure:

Hydantoin **1** (500 mg, 5.00 mmol) in a 100-mL flask was exposed to NO_2 gas (490 mg, 10.7 mmol) from a 500-mL flask at a vacuum line overnight at room temperature. The nitramine **2** (725 mg, 5.00 mmol; mp 174 °C) was obtained quantitatively after collection of the gases of reaction in a trap at 77 K and drying of the solid.

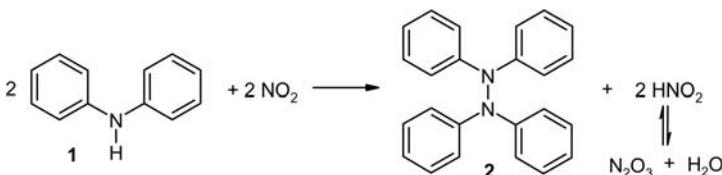
The N_2O_3 and N_2O_4 condensates in the cold trap were treated with dry air at -30 to -20°C for a complete oxidative recovery of solid N_2O_4 for further use as gaseous NO_2 .

References: G. Kaupp, J. Schmeyers, *J. Org. Chem.*, **60**, 5494 (1995).

Type of reaction: N–N bond formation

Reaction condition: solid state

Keywords: gas-solid reaction, oxidative coupling, diphenylamine, tetraphenylhydrazine



Experimental procedure:

Diphenylamine **1** (338 mg, 2.00 mmol) in an evacuated 250-mL flask at 0°C was exposed to NO_2 gas (370 mg, 8.0 mmol) that was slowly added from a 300-mL funnel through an adjusted stopcock over 4–6 h. After 12 h the gases of reaction were condensed to a cold trap at 77 K and the product evacuated for 2 h at 5×10^{-4} Torr. Colorless **2** (309 mg, 92%), mp 168–173 °C dec., was obtained after sublimation of the initially green product at 5×10^{-4} Torr.

The N_2O_3 and N_2O_4 condensates in the cold trap were treated with dry air at -30 to -20°C for a complete oxidative recovery of solid N_2O_4 for further use as gaseous NO_2 .

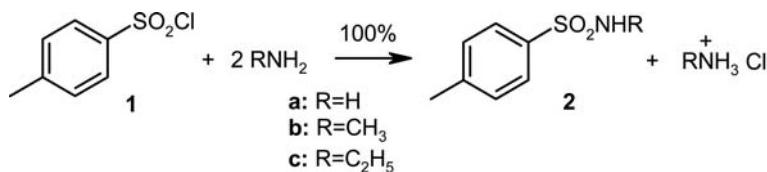
References: M.R. Naimi-Jamal, H. Hamzeali, J. Mokhtari, J. Boy, G. Kaupp, submitted to *ChemSusChem* (2008).

9.2 Solvent-Free N–S Bond Formation

Type of reaction: S–N bond formation

Reaction condition: solid-state

Keywords: gas-solid reaction, *p*-toluenesulfonylchloride, *p*-toluenesulfonamide



Experimental procedure:

Solid *p*-toluenesulfonylchloride **1** (1.00 mmol) in an evacuated 100-mL flask was exposed to the amine gas (0.5 bar). After 2 h the excess gas was condensed to a trap at 77 K and the quantitatively obtained **2** washed with water and dried in a good vacuum.

References: G. Kaupp, *Top. Curr. Chem.*, **254**, 95 (2005).

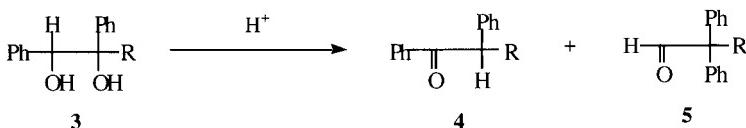
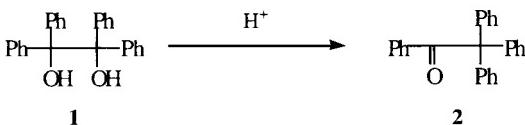
10 Rearrangement

10.1 Solvent-Free Rearrangement

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: 1,2-diol, *p*-TsOH, pinacol rearrangement, ketone



- a: R=Ph
- b: R=2-MeC₆H₄
- c: R=3-MeC₆H₄
- d: R=4-MeC₆H₄
- e: R=4-MeOC₆H₄
- f: R=4-ClC₆H₄

Experimental procedures:

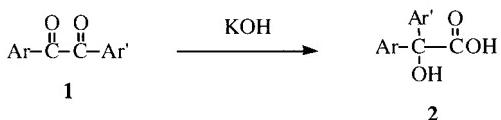
When a mixture of 1:3 molar ratio of powdered **3** and *p*-TsOH was kept at 60 °C for 2.5 h, products **4** and **5** were obtained in 89 and 8% yields, respectively.

References: F. Toda, T. Shigemasa, *Chem. Commun.*, 209 (1989).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: benzil, alkyl metal hydroxide, benzylic acid rearrangement, benzylic acid



- a: Ar=Ph; Ar'=Ph
- b: Ar=Ph; Ar'=4-ClC₆H₄
- c: Ar=4-ClC₆H₄; Ar'=4-ClC₆H₄
- d: Ar=Ph; Ar'=4-NO₂C₆H₄
- e: Ar=3-NO₂C₆H₄; Ar'=3-NO₂C₆H₄
- f: Ar=Ph; Ar'=4-MeOC₆H₄
- g: Ar=Ph; Ar'=3,4-(OCH₂O)C₆H₃
- h: Ar=4-MeOC₆H₄; Ar'=4-MeOC₆H₄
- i: Ar=3,4-CH₂O₂C₆H₃; Ar'=3,4-(OCH₂O)C₆H₃

Experimental procedures:

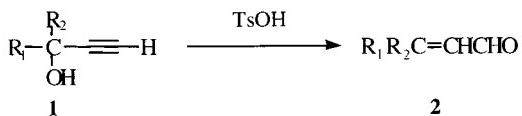
A mixture of finely powdered benzil **1a** (0.5 g, 2.38 mmol) and KOH (0.26 g, 4.76 mmol) was heated at 80 °C for 0.2 h, and the reaction product was mixed with 3N HCl (20 mL) to give benzylic acid **2a** as colorless needles (0.49 g, 90% yield).

References: F. Toda, K. Tanaka, Y. Kagawa, Y. Sakaino, *Chem. Lett.*, 373 (1990).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: propargyl alcohol, TsOH, Meyer-Schuster rearrangement, cinnamic aldehyde



- a: R₁=R₂=Ph
- b: R₁=Ph; R₂=2-ClC₆H₄
- c: R₁=R₂=2,4-Me₂C₆H₃

Experimental procedures:

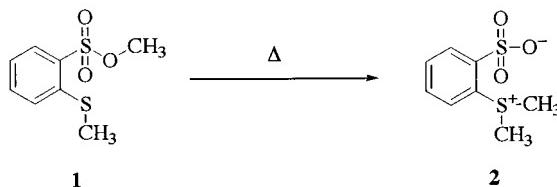
The reaction was carried out by keeping a mixture of powdered **1** and an equimolar amount of TsOH at 50 °C for 2–3 h.

References: F. Toda, H. Takumi, M. Akehi, *Chem. Commun.*, 1270 (1990).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: methyl 2-(methylthio)benzenesulfonate, rearrangement, 2-(dimethylsulfonium)benzenesulfonate



Experimental procedures:

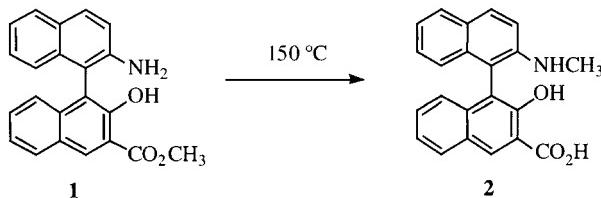
Powdered samples of **1** were kept at various temperatures between 36 and 49 °C (mp 54–55 °C) for various periods. The ratio of **2** to **1** was estimated by ^1H NMR measurement of the product dissolved in $\text{d}_6\text{-DMSO}$. In one experiment, ca. 12–13% transformation of **1** to **2** occurred after 28 days (14 days at 36 °C and 14 days at 49 °C); in another, 32% transformation occurred after 20 days at 45 °C.

References: P. Venugoplalan, K. Venkatesan, J. Klausen, E. Novotny-Bregger, C. Leumann, A. Eshenmoser, J.D. Dunitz, *Helv. Chim. Acta.*, **74**, 662 (1991).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: 2-amino-2'-hydroxy-3'-(methoxycarbonyl)-1,1'-binaphthyl, $\text{S}_{\text{N}}2$ substitution, 2-methylamino-2'-hydroxy-3'-carboxy-1,1'-binaphthyl



Experimental procedures:

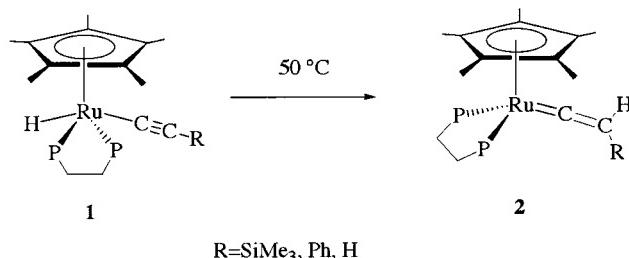
Crystalline (\pm)-**1** (343 mg) was heated under argon in a sealed tube at 150 ± 2 °C for 30 min (to reach full conversion). The product was chromatographed on silica gel (20 g) using a $\text{CHCl}_3\text{-MeOH}$ mixture (1:1) as eluent to give pure **2** (325 mg, 95%).

References: M. Smrcina, S. Vyskocil, V. Hanus, M. Polasek, V. Langer, B.G.M. Chew, D.B. Zax, H. Verrier, K. Harper, T.A. Claxton, P. Kovacs, *J. Am. Chem. Soc.*, **118**, 487 (1996).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: hydrido complex, ruthenium, tautomerization, vinylidene complex



Experimental procedures:

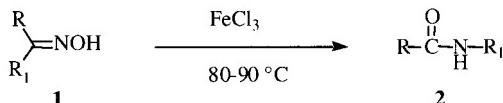
In the case of $[(C_5Me_5RuH(C\equiv CH)(dippe)][BPh_4]$ **1**, which does not rearrange at an appreciable rate at 25 °C, the sample was kept in an oven at 50±3 °C. At regular time intervals, the sample was taken out, and its IR spectrum was recorded at room temperature. After recording each spectrum, the sample was returned back to the oven, and the cycle was repeated over a period of 10 h. After 21 h at 50±3 °C, conversion to $[(C_5Me_5RuH(C=CHR)(dippe)][BPh_4]$ **2** was found to be complete.

References: E. Bustelo, I. de los Rios, M.J. Tenorio, M.C. Puerta, P. Valerga, *Monatsh. Chem.*, **131**, 1311 (2000).

Type of reaction: rearrangement

Reaction condition: solvent-free

Keywords: ketoximes, Beckmann rearrangement, FeCl₃, amides



- a: R, R₁=-(CH₂)₅-
- b: R, R₁=-(CH₂)₇-
- c: R, R₁=-(CH₂)₁₁-
- d: R=R₁=Ph
- e: R=R₁=CH(CH₃)₂
- f: R=CH₃; R₁=CH₂CH(CH₃)₂
- g: R=CH₃; R₁=Ph
- h: R=CH₃; R₁=4-CH₃C₆H₄

Experimental procedures:

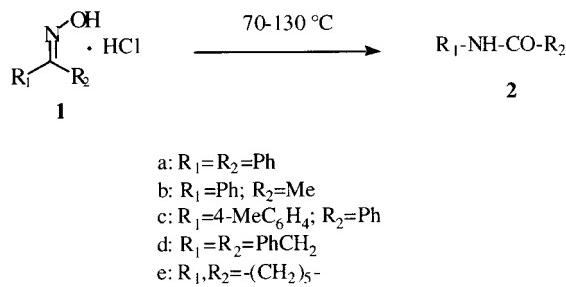
The oxime (10 mmol) and FeCl_3 (30–40 mmol) were mixed in a mortar. The reaction mixture was allowed to stand at 80–90 °C for 1.5–3 h. The progress of reaction was followed by dissolving a sample in acetone and monitoring on silica gel plates (SIL G/UV 254 plates). Water (15 mL) was added and the whole extracted with chloroform (3×20 mL). Drying and evaporation of the solvent gave the products in 81–95% yields which recrystallized from *n*-heptane.

References: M.M. Khodaei, F.A. Meybodi, N. Rezai, P. Salehi, *Synth. Commun.*, **31**, 2047 (2001).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: oxime, Beckmann rearrangement, nitrile ylide, amide



Experimental procedures:

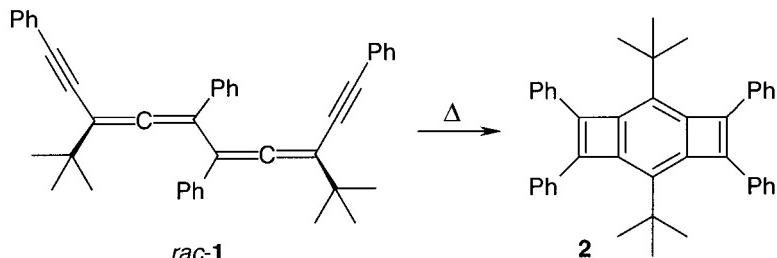
A stirred solution of the oxime **1** (1 g) in dry diethyl ether (20 mL), in a 100-mL two-necked round-bottomed flask protected by a CaCl_2 guard tube, was saturated with dry hydrogen chloride gas via an inlet. A white solid precipitated out, which was allowed to settle and collected by pipetting out the supernatant ether under nitrogen, and removing trace volatiles in *vacuo*. A pinch was transferred under nitrogen to a melting point capillary, which was then fully sealed before the determination of the mp. The rest was heated under nitrogen as indicated, the reaction being followed by TLC. The darkened solid was cooled and taken into ether; the resulting solution was washed successively with NaHCO_3 solution and water, dried (MgSO_4) and the solvent evaporated in *vacuo*. The products **2** were purified by recrystallization and identified by their mp's, IR and ^1H NMR spectra.

References: S. Chandrasekhar, K. Gopalaiah, *Tetrahedron Lett.*, **42**, 8123 (2001).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: bisallene, ene-ine, cycloaddition, thermolysis, benzocyclobutene



Experimental procedure:

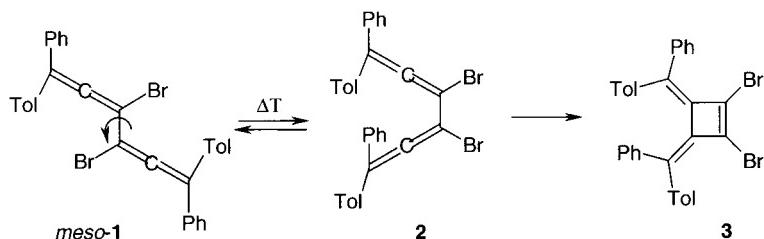
The crystalline micronized bisallene **rac-1** was heated to 140–150 °C in a vacuum. The crystals turned dark-green and the reaction was completed within 4 h. Product **2** (20–28%) was very sensitive to oxygen. Supermicroscopy (AFM) revealed that the reaction occurred only at outer and inner surfaces.

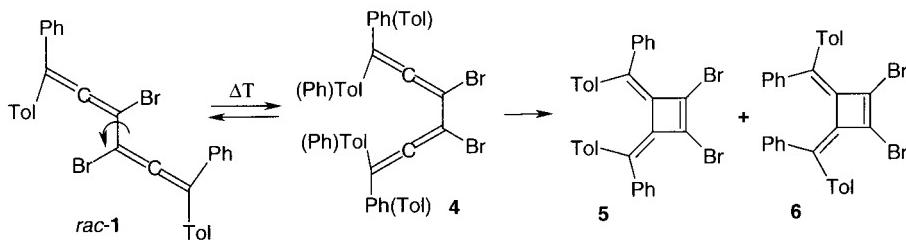
References: F. Toda, *Eur. J. Org. Chem.*, 1377 (2000); G. Kaupp, J. Schmeyers, M. Kato, K. Tanaka, N. Harada, F. Toda, *J. Phys. Org. Chem.*, **14**, 444 (2001).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: bisallene, cyclization, stereospecific, thermolysis, bismethylene-cyclobutene



**Experimental procedures:**

The bisallene *meso*-**1** (0.20 g) was heated to 135 °C for 90 min. A quantitative yield of **3** was obtained (mp 214–215 °C, EtOAc).

Similarly, *rac*-**1** (0.40 g) was heated to 125 °C for 90 min. The quantitatively formed 1:1 mixture of **5** and **6** was fractionally crystallized to give pure **5** (mp 180–183 °C) and pure **6** (mp 215–218 °C).

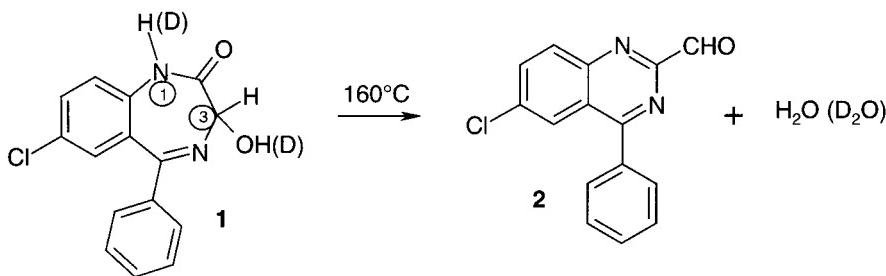
The stereochemistry proves the occurrence of the intermediates **2** and **4**, respectively. These reactions were also studied by supermicroscopy (AFM) (Ref. 2).

References: (1) F. Toda, K. Tanaka, T. Tamashima, M. Kato, *Angew. Chem.*, **110**, 2852 (1998); *Angew. Chem. Int. Ed. Engl.*, **37**, 2724 (1998); (2) G. Kaupp, J. Schmeyers, M. Kato, K. Tanaka, F. Toda, *J. Phys. Org. Chem.*, **15**, 1 (2002).

Type of reaction: rearrangement

Reaction condition: solvent-free

Keywords: oxazepam, [1,3,2,3]-elimination, quinazoline aldehyde

**Experimental procedures:**

The tranquilizer oxazepam **1** (mp 200–205 °C; 1.00 g, 3.5 mmol) was heated to 160 °C for 2 h. The water escaped and a quantitative yield of the aldehyde **2** (mp 176 °C) was obtained. The product **2** was sticky at 160 °C. Thus, the initial solid-state reaction changed to a (partial) melt reaction as it proceeded. It was not nec-

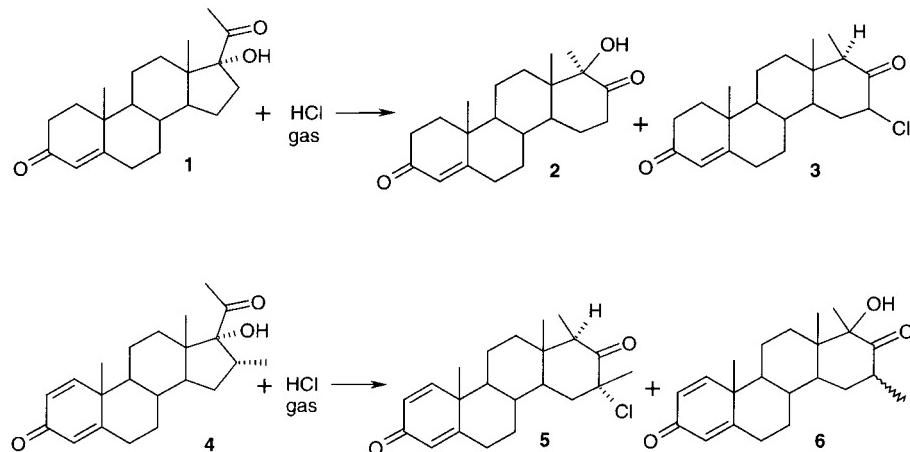
essary to use solvent or a sealed tube. The mechanism was discussed on the basis of the deuteration experiment.

References: G. Kaupp, B. Knichala, *Chem. Ber.*, **118**, 462 (1985).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: 17 α -hydroxy-20-ketosteroid, acyloin rearrangement, substitutive rearrangement, stereoselective, gas-solid reaction



Experimental procedures:

17 α -Hydroxyprogesterone **1** (1.98 g, 6.0 mmol) were co-ground with 4.0 g MgSO₄·2.3 H₂O. The mixture was treated with HCl (1 bar) in an evacuated 500-mL flask at room temperature for 16 h. Excess gas was recovered in a cold trap at -196 °C and the organic material extracted with CH₂Cl₂. The raw material (2.09 g) contained **2** and **3** in a 1:1 ratio and 8% of the dehydration product of **1** without ring enlargement. The sensitive products were separated by preparative TLC on 400 g SiO₂ with CH₂Cl₂-EtOAc (1:5) to give pure **2** (320 mg, 16%; mp 183–185 °C, diisopropyl ether) and **3** (820 mg, 44%; mp 189–193 °C, benzene).

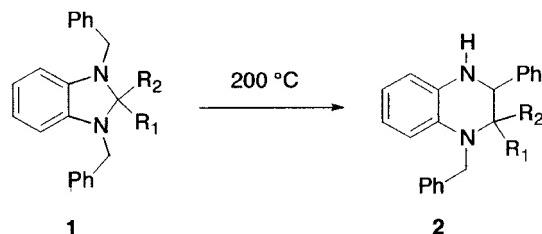
Similarly, **4** (270 mg, 0.88 mmol) was treated with 0.9 bar HCl in a 100-mL flask at 4 °C for 4 days (no drying agent). Excess gas was pumped off and preparative TLC on 200 g SiO₂ with CH₂Cl₂-EtOAc (5:1) yielded 62% **5**, 20% unchanged **4** and **6** (2 stereoisomers). The latter stereoisomers **6** prevailed if the reaction was performed in the presence of 1.0 g MgSO₄·2.3 H₂O.

References: G. Kaupp, E. Jaskulska, G. Sauer, G. Michl, *J. Prakt. Chem.*, **336**, 686 (1994).

Type of reaction: rearrangement

Reaction condition: solvent-free

Keywords: benzimidazoline, melt reaction, tetrahydrobenzopyrazine



a: R ¹ =R ² =Me	(11%)
b: R ¹ =Me, R ² =Et	(13%)
c: R ¹ =Me, R ² =Pr	(10%)
d: R ¹ , R ² =(CH ₂) ₅	(16%)
e: R ¹ , R ² =(CH ₂) ₄	(14%)

Experimental procedures:

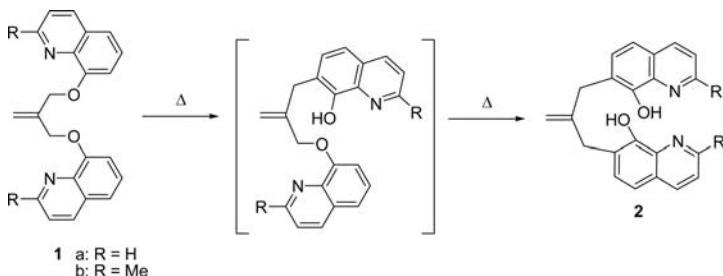
The 2,2-dialkylbenzimidazoline **1** was heated to 200°C in a sealed tube and the rearranged product **2** was isolated by column chromatography with petroleum ether.

References: C.M. Reddy, P.L. Prasunamba, P.S.N. Reddy, *Tetrahedron Lett.*, **37**, 3355 (1996).

Type of reaction: rearrangement

Reaction condition: solvent-free

Keywords: Claisen rearrangement, 1,1-bis(aryloxy methyl)ethylene



Experimental procedures:

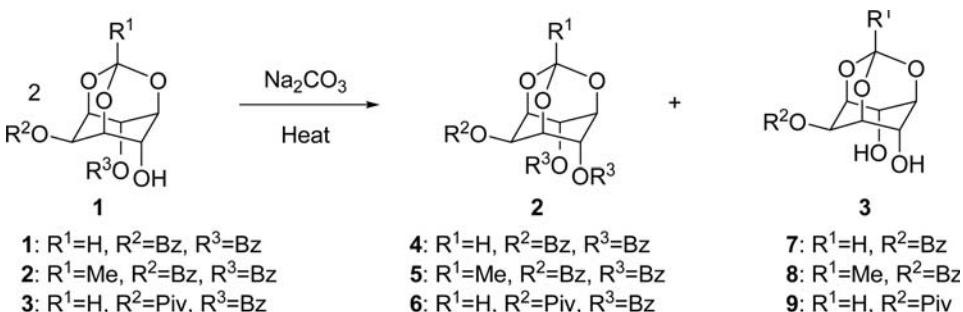
The pyrolytic reaction of **1** (0.6 g) was carried out in a 20-mL round-bottomed flask at 200 °C for 2 h without solvent under nitrogen atmosphere. The residue was subjected to column chromatography on silica gel with chloroform as eluent to give **2** (0.54 g) as a main product.

References: K. Hiratani, T. Takahashi, K. Kasuga, H. Sugihara, K. Fujiwara, K. Ohashi, *Tetrahedron Lett.*, **36**, 5567 (1995).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: inositol, transesterification

**Experimental procedures:**

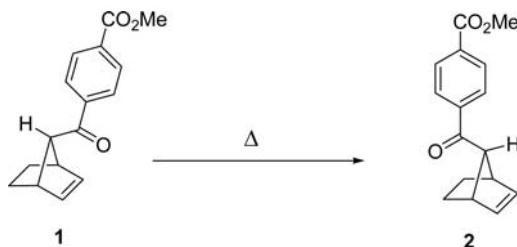
The dibenzoate **2** (0.500 g, 1.250 mmol) and sodium carbonate (1.060 g, 10.0 mmol) were ground together and heated at 140 °C in an atmosphere of nitrogen for 168 h. Isolation of the products as mentioned in the general procedure gave **5** (0.125 g, 19%), 4,6-di-*O*-benzoyl-myo-inositol 1,3,5-orthoacetate (0.040 g, 8%), **8** (0.080 g, 21%), *racemic* 4-*O*-benzoyl-myo-inositol 1,3,5-orthoacetate (0.060 g, 16%), and the starting material **2** (0.070 g, 14%).

References: M.P. Sarmah, R.G. Gonnade, M.S. Shashidhar, M.M. Bhadbhade, *Chem. Eur. J.*, **11**, 2103 (2005).

Type of reaction: Rearrangement

Reaction condition: solid-state

Keywords: retro-Claisen rearrangement

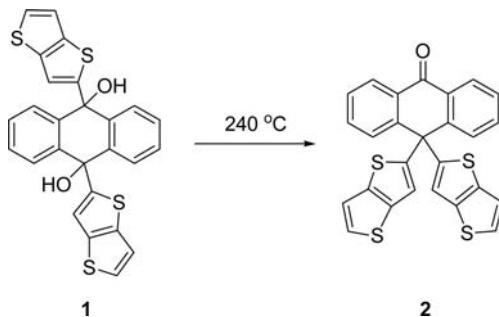
**Experimental procedures:**

Ketone **1** (40 mg, 0.16 mmol) was placed in a sealed tube and heated at 210 °C in a sand bath for 52 h. The reaction mixture was separated on a silica gel column to afford starting material (23 mg) and the isomeric product **2** (16 mg), mp 113–115 °C.

References: W. Xia, C. Yang, B.O. Patrick, J.R. Scheffer, C. Scott, *J. Am. Chem. Soc.*, **127**, 2725 (2005).

Type of reaction: Rearrangement**Reaction condition:** solid-state

Keywords: 1,4-pinacol type rearrangement, 9,10-dihydroxy-9,10-dihydroanthracene

**Experimental procedures:**

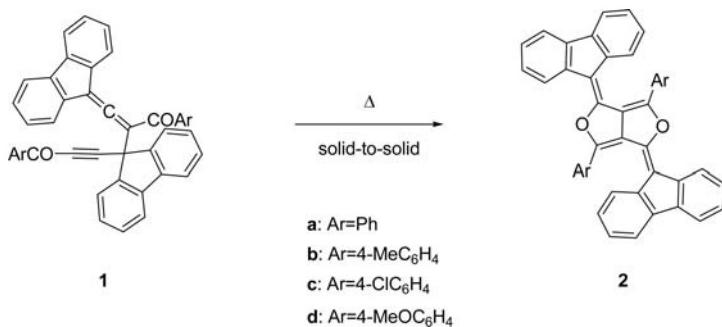
Compound **1** (3.1 g, 6.3 mmol) was heated to 250 °C on a hot plate equipped with a thermometer under a stereomicroscope to yield **2** (2.92 g, 6.2 mmol) in quantitative yield.

References: R. Sekiya, K. Kiyo-oka, T. Imakubo, K. Kobayashi, *J. Am. Chem. Soc.*, **122**, 10282 (2000).

Type of reaction: Rearrangement

Reaction condition: solid-state

Keywords: propargylallene, furofuran, solid-to-solid reaction



Experimental procedures:

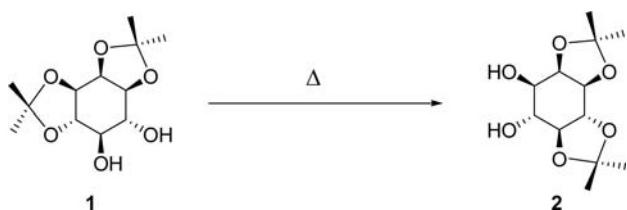
Heating of 100 mg of **1a-d** in the solid state at 198 °C for 30 min afforded 100 mg of **2a-d** as dark copper-brown prisms. **2a:** mp 293–295 °C; **2b:** mp 295–296 °C; **2c:** mp 292–294 °C; **2d:** mp 243–245 °C.

References: K. Tanaka, A. Tomomori, J.L. Scott, *Eur. J. Org. Chem.*, 2035 (2003).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: transketolization, 1,2:3,4-di-*O*-isopropylidene-myo-inositol



Experimental procedures:

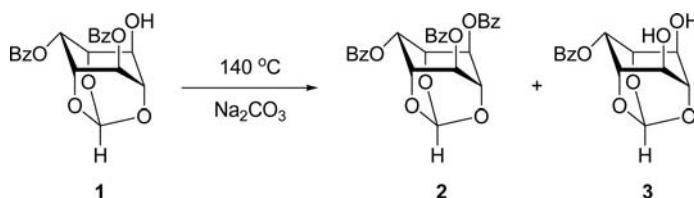
Heating the crystals of **1** at 110 °C for 10 min effected a 92–95% isomerization.

References: K.M. Sureshan, T. Murakami, T. Miyasou, Y. Watanabe, *J. Am. Chem. Soc.*, **126**, 9174 (2004).

Type of reaction: Rearrangement

Reaction condition: solid-state

Keywords: 2,4-Di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate, transesterification



Experimental procedures:

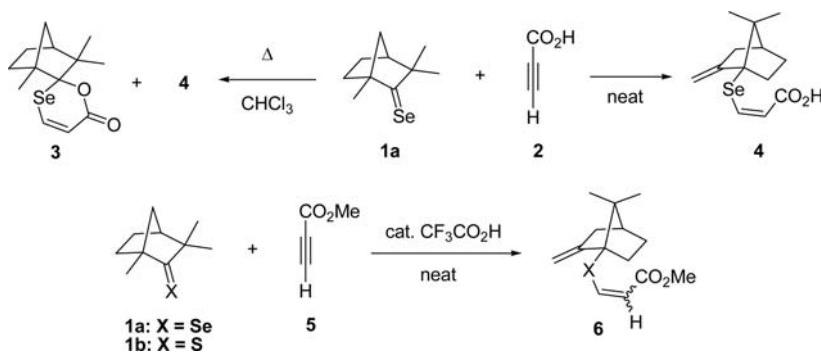
The dibenzoate **1** (0.100 g, 0.25 mmol) and sodium carbonate (0.212 g, 2.0 mmol) were ground together using a pestle and mortar, and the resulting mixture was heated at 140 °C in an atmosphere of argon for 60 h. The solid obtained after the reaction was cooled to ambient temperature and extracted with chloroform followed by methanol. The combined organic extract was evaporated to dryness: the products **2** (0.06 g, 47%) and **3** (0.036 g, 49%) were isolated by column chromatography over silica gel (eluent: ethyl acetate–light petroleum, gradient elution) and characterized by comparison (TLC, mp, IR, and NMR spectra) with authentic samples.

References: T. Praveen, U. Samanta, T. Das, M.S. Shashidhar, P. Chakrabarti, *J. Am. Chem. Soc.*, **120**, 3842 (1998); M.P. Sarmah, R.G. Gonnade, M.S. Shashidhar, M.M. Bhadbhade, *Chem. Eur. J.*, **11**, 2103 (2005).

Type of reaction: rearrangement

Reaction condition: solvent-free

Keywords: selenofenchone, propiolic acid, Wagner-Meerwein rearrangement



Experimental procedures:

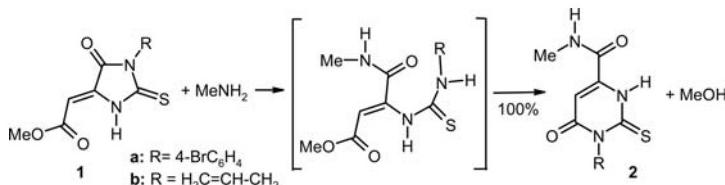
To a solution of **1a** in chloroform was added propiolic acid. After refluxing for 16 h, the reaction mixture was evaporated to afford a pale yellow oil, which was chromatographed over silica gel to afford selenodioxenone **3** and rearranged product **4**. When the reaction of **1a** with propiolic acid (3 equiv.) was carried out under solvent-free conditions, only the rearranged product **4** was obtained in 97% yield.

References: K. Okuma, Y. Mori, T. Shigetomi, M. Tabuchi, K. Shioji, Y. Yokomori, *Tetrahedron Lett.*, **48**, 8311 (2007).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: gas-solid reaction, methylamine, methylenethiohydantoins, 2-thioorotic acid amides, cascade reaction

**Experimental procedures:**

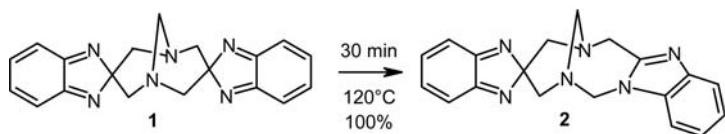
3-Bromophenyl- or 3-allyl-5-methoxycarbonylmethylidene-2-thiohydantoin **1** (1.00 g, 2.94 or 4.42 mmol) in a 250-mL flask was exposed to methylamine gas (1 bar) overnight at room temperature. Excess gas was collected in a cold trap at 77 K and the methanol of reaction evaporated at 80 °C in a vacuum to obtain quantitative yields of the 2-thioorotic acid amides **2a** (mp 280 °C, dec.) or **2b** (mp 153 °C).

References: G. Kaupp, J. Schmeyers, A. Kuse, A. Atfeh, *Angew. Chem. Int. Ed. Engl.*, **38**, 2896 (1999).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: thermolysis, quantitative, [1,5]-shift, dispiro-methano-1,5-diazocine, spiro-methano-1,3,6-triazonine

**Experimental procedure:**

The compound **1** (100 mg, 0.3 mmol; mp 132 °C with rearrangement) was heated to 120 °C for 30 min in a vacuum. The product **2** (mp 229 °C) was obtained quantitatively.

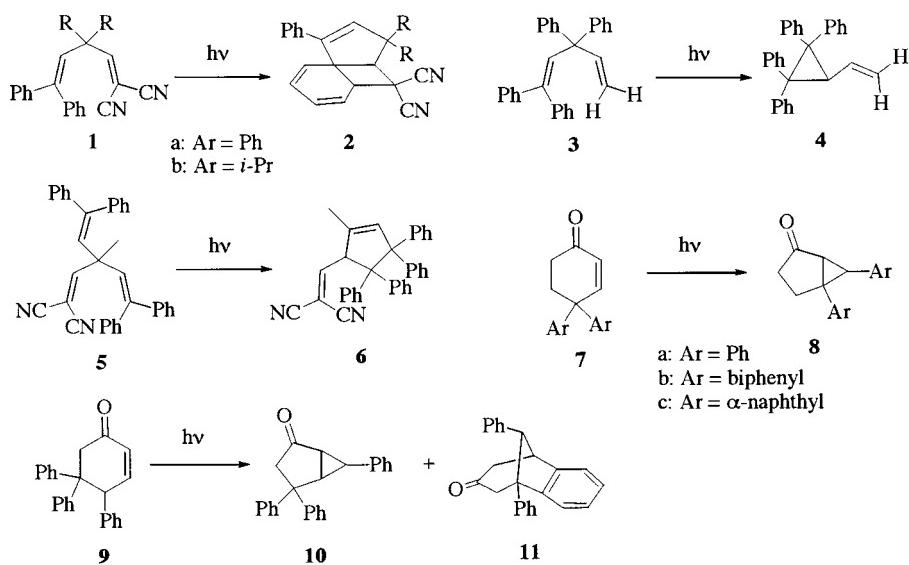
References: G. Kaupp, K. Sailer, *J. prakt. Chem.*, **338**, 47 (1996).

10.2 Solvent-Free Rearrangement under Photoirradiation

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: 1,4-pentadiene derivatives, 2-cyclohexenone derivatives, di- π -methane rearrangement, photoirradiation



Experimental procedures:

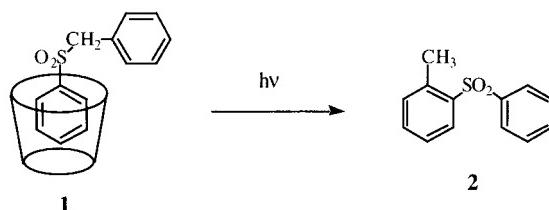
A crystalline film of 314 mg (0.744 mmol) of 1,1,3,3-tetraphenyl-5,5-dicyano-1,4-pentadiene **1a**, deposited by slow evaporation of a 20% ether in hexane solution, was irradiated at 78 °C for 2.5 h through Pyrex. The resulting orange-red solid was subjected to preparative HPLC eluted with 8% ether and 0.5% acetonitrile in hexane to give 227.1 mg (72.3%) of starting diene and 74.8 mg (23.8%) of **2a** as a pale purple-red solid. Recrystallization from ether-hexane yielded 69.7 mg (21.6%) of **2a** as a white solid (mp 125–128 °C).

References: H.E. Zimmerman, M.J. Zuraw, *J. Am. Chem. Soc.*, **111**, 7974 (1989); H.E. Zimmerman, Z. Zhu, *J. Am. Chem. Soc.*, **117**, 5245 (1995); H.E. Zimmerman, E.E. Nesterov, *J. Am. Chem. Soc.*, **124**, 2812 (2002).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: benzyl phenyl sulfone, β -cyclodextrin, photorearrangement, 2-methyl-phenyl phenyl sulfone



Experimental procedures:

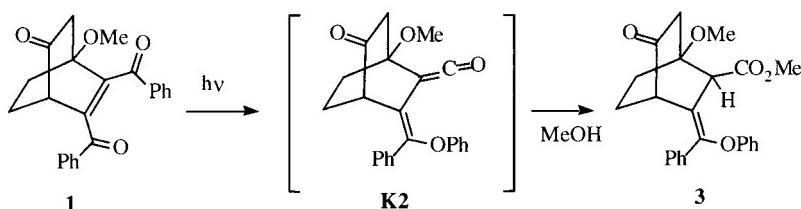
The solid 1:1 complex of **1** with β -cyclodextrin was irradiated for 100 h. Photo-products were identified using GC by coinjection of authentic samples synthesized separately and also by their ^1H NMR spectra.

References: K. Pitchumani, P. Velusamy, H.S. Banu, C. Srinivasan, *Tetrahedron Lett.*, **36**, 1149 (1995).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: *cis*-1,2-dibenzoylalkene, photorearrangement, keten, enoether

**Experimental procedures:**

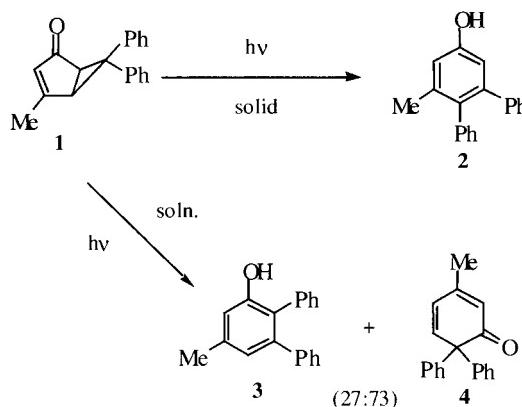
An emulsion of **1** (1 g, 2.77 mmol) in distilled water (150 mL) was irradiated using a 450-W medium-pressure Hanovia lamp and a Pyrex filter for 36 h with stirring. The photolyzed mixture was extracted with dichloromethane. Removal of the solvent in vacuo gave a thick residue. It was then stirred with methanol for about 6 h. Solvent was removed in vacuo to give a residue that was chromatographed over a silica gel column. Elution with a mixture of 15% ethyl acetate in PE gave **3** as a white solid, mp 41 °C (230 mg, 21%), which was crystallized with difficulty from a mixture of *n*-pentane and dichloromethane (4:1).

References: D. Maji, R. Singh, G. Mostafa, S. Ray, S. Lahiri, *J. Org. Chem.*, **61**, 5165 (1996).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: bicyclo[3.1.0]hex-3-en-2-one, photorearrangement, phenol



Experimental procedures:

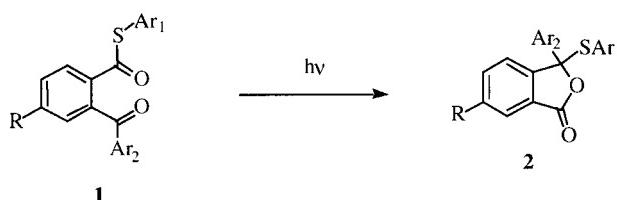
Crystals were spread over a strip of "Parafilm". Both the photochemical reactor and the strip with crystals were placed in a drybox and purged with nitrogen for 1 h. A 40 mg portion of 4-methyl-6,6-diphenylbicyclo[3.1.0]hex-3-en-2-one **1** was irradiated under conditions described above for 10 min through a 5 mm filter solution of 10⁻³ M sodium metavanadate in 5% sodium hydroxide. The mixture was chromatographed on preparative TLC plate eluted with 7% ether in hexane. Band **1** (28.0 mg, 70%) contained 3-methyl-4,5-diphenylphenol **2**. Crystallization from hexane gave 14.1 mg (35%) of colorless crystals, mp 109–110°C.

References: H. E. Zimmerman, P. Sebek, *J. Am. Chem. Soc.*, **119**, 3677 (1997).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: *S*-aryl-*o*-arylbenzothioate, chiral crystal, photoirradiation, 1,4-aryl migration, phthalide



30~87% ee

- a: R=H, Ar₁=(*o*-tol), Ar₂=Ph
- b: R=H, Ar₁=Ph, Ar₂=Ph
- c: R=H, Ar₁=(*m*-tol), Ar₂=Ph
- d: R=H, Ar₁=(*p*-tol), Ar₂=Ph
- e: R=Me, Ar₁=Ph, Ar₂=Ph
- f: R=H, Ar₁=Ph, Ar₂=(*p*-tol)
- g: R=H, Ar₁=Ph, Ar₂=(*p*-ClPh)

Experimental procedures:

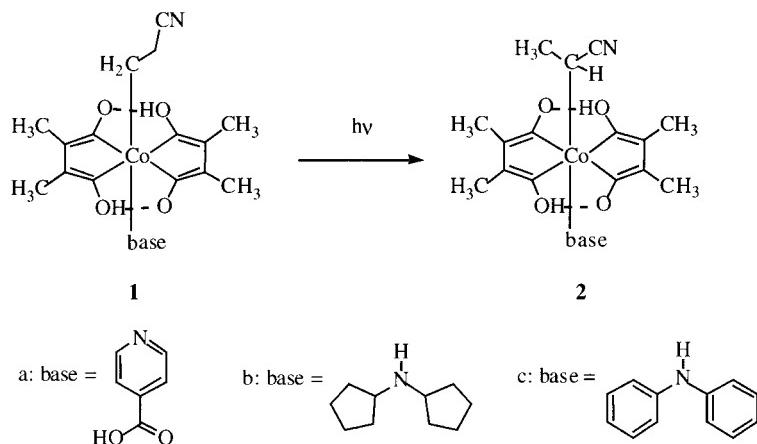
All samples were well ground and sandwiched between two Pyrex slides. The crystal samples packed in polyethylene bags in order to prevent soaking were purged by dried nitrogen, and were then closed in vacuo. They were placed in a cooling bath close to the light source. All crystal samples were irradiated with an Eikosha 500-W high-pressure mercury lamp. After irradiation, the photolysates were treated the same as that in solution photochemistry. The enantiomeric purities of **2a–c** were determined by preparative HPLC using Chiralcell OJ (Daicel) with an eluent of EtOH-hexane (4:1).

References: M. Takahashi, N. Sekine, T. Fujita, S. Watanabe, K. Yamaguchi, M. Sakamoto, *J. Am. Chem. Soc.*, **120**, 12770 (1998); M. Sakamoto, M. Takahashi, S. Moriizumi, K. Yamaguchi, F. Fujita, S. Watanabe, *J. Am. Chem. Soc.*, **118**, 8138 (1996).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: 2-cyanoethyl-isonicotinic acid-cobaltoxime complex, photoisomerization, 1-cyanoethyl-isonicotinic acid-cobaltoxime complex



Experimental procedures:

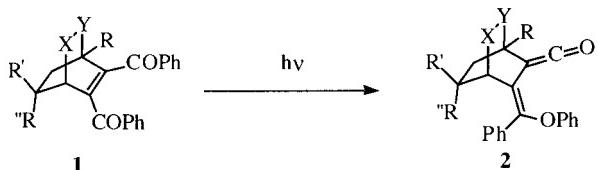
A KBr disk which contained 1% of the samples was exposed to a 500-W xenon lamp (Ushio UXL-5S+UI-501 C), the distance between the disk and the lamp being 20 cm. The absorption assigned to the stretching vibrational mode of the cyano group of the 2-cyanoethyl complex, ν_{CN} , is at 2250 cm^{-1} , whereas ν_{CN} of the 1-cyanoethyl complex is at 2200 cm^{-1} . The infrared spectra of KBr disks including the powdered samples of crystals I, II and III were measured at a constant interval of 10 min, using a JASCO A-1000 IP spectrometer. The decrease of the absorption band at 2250 cm^{-1} within 40 min was explained by first-order kinetics for each sample and its rate constant was obtained by least-squares fitting. The rates for I, II and III were 1.88 , 1.33 and $2.76 \times 10^{-4} \text{ s}^{-1}$, respectively.

References: D. Hashizume, Y. Ohashi, *J. Chem. Soc., Perkin Trans. 2*, 1931 (1998).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: *cis*-1,2-dibenzoylalkene, photoirradiation, vinylketene



- a: X=CO; Y=CH₂; R=OMe; R'=R''=H
- b: X=CO; Y=CH₂; R=Me; R'=R''=H
- c: X=CH₂; Y=CO; R=Me; R'=R''=H
- d: X=CO; Y=CH₂; R=R'=R''=Me

Experimental procedures:

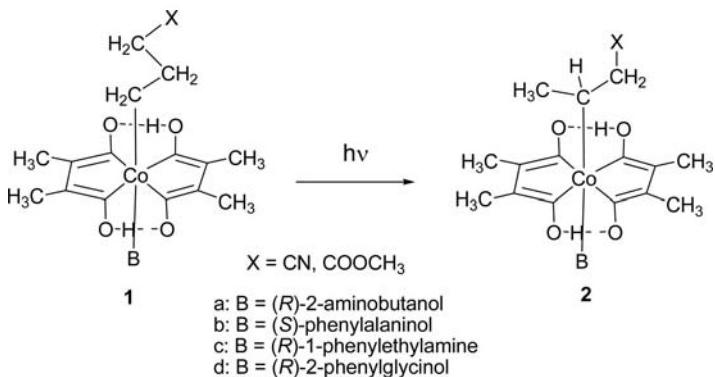
A suspension of the compound (0.5–1 g) in distilled water (150 mL) was irradiated with stirring using a Hanovia medium-pressure 450-W lamp and a Pyrex filter for ca. 35 h. The suspension was then extracted with CH₂Cl₂ and the residue obtained after removal of solvent was chromatographed on a silica gel column (60–120 mesh). The ketene was eluted with a mixture of ethyl acetate (5–10%) in petroleum ether (bp 60–80 °C).

References: M. Chanda, D. Maji, S. Lahiri, *Chem. Commun.*, 543 (2001).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: photoisomerization, cobalt complex, single-crystal-to-single-crystal



Experimental procedures:

51.4 mg of crystals, **1c**, was suspended in 2.5 mL of nujol and powdered by a grinder for 10 min. The suspended sample was transferred to a petri dish, diameter 8.8 cm, and a trace amount of the residue left on the dish was washed twice with another 2 ml of nujol and transferred into the same petri dish. The sample suspended in nujol was irradiated with a solar simulator (Flux density:

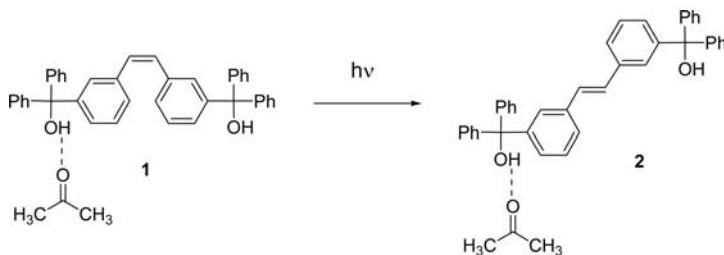
100 mW cm⁻²) for 8 h. The reaction products were filtered and the nujol was washed out with hexane to give 39.5 mg of crystals.

References: Y. Ohgo, K. Ishida, Y. Hiraga, Y. Arai, S. Takeuchi, *J. Organometallic Chem.*, **691**, 2319 (2006).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: cis-trans photoisomerization, 3,3'-bis(diphenylhydroxymethyl)stilbene



Experimental procedures:

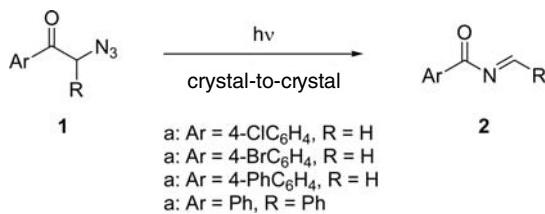
Solid-state photolysis of the powdered 1:1 acetone complex of **1** (0.20 g, 0.38 mmol) for 6 h using a 400 W high-pressure Hg lamp gave crude crystals of the 1:1 acetone complex of **2** with 92% conversion.

References: K. Tanaka, T. Hiratsuka, S. Ohba, M.R. Naimi-Jamal, G. Kaupp, *J. Phys. Org. Chem.*, **16**, 905 (2003).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: *a*-azidoacetophenone, benzamide



Experimental procedures:

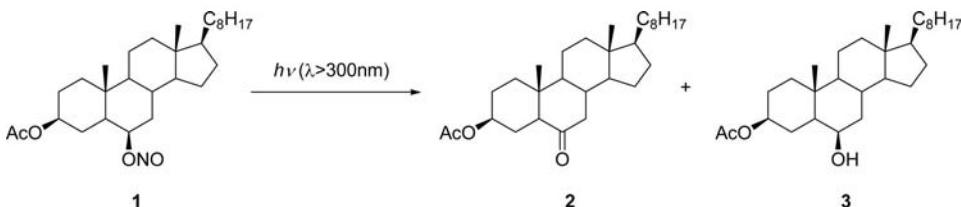
Crystals of azide **1** (~1 mmol) were dried under vacuum for a period of 24 h. The dried crystals were stored in Pyrex test tubes which were flushed with argon for 15 min and sealed. The solid samples were photolyzed for 12 h in an ice-bath. The reacted crystals were dissolved in anhydrous ethyl acetate. GC-MS analysis of the reaction mixture showed formation of **2** only and no remaining starting material.

References: S.M. Mandel, P.N.D. Singh, S. Muthukrishnan, M. Chang, J.A. Krause, A.D. Gudmundsdóttir, *Org. Lett.*, **8**, 4207 (2006).

Type of reaction: rearrangement

Reaction condition: solid-state

Keywords: alkyl nitrite, ketone

**Experimental procedures:**

When, 6-nitroso-oxy-5-cholestane-3-yl acetate (**1**) was irradiated by a 500-W super-high-pressure mercury lamp for 24 h through a cut-off filter (>300 nm) in the solid state, ketone **2** and alcohol **3** were obtained in 50% and 16% yields, respectively.

References: K. Kinbara, H. Takezaki, A. Kai, K. Saigo, *Chem. Lett.*, **25**, 217 (1996).

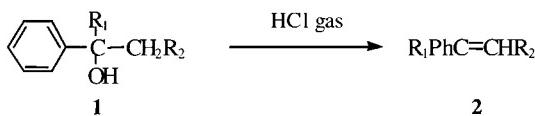
11 Elimination

11.1 Solvent-Free Elimination

Type of reaction: elimination

Reaction condition: gas-solid

Keywords: alcohol, HCl gas, dehydration, alkene



- a: R₁=Ph; R₂=H
- b: R₁=Ph; R₂=Me
- c: R₁=Ph; R₂=Ph
- d: R₁=Ph; R₂=2-NO₂C₆H₄
- e: R₁=2-ClC₆H₄; R₂=Me

Experimental procedures:

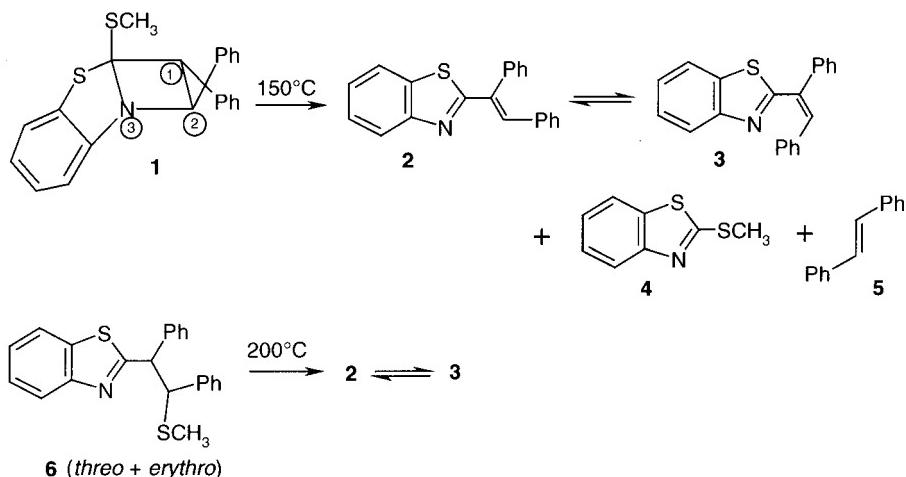
Powdered 1,1-diphenylpropan-1-ol **1b** kept in a desiccator filled with HCl gas for 5.5 h gave pure 1,1-diphenylprop-1-ene **2b** in 99% yield.

References: F. Toda, H. Takumi, M. Akehi, *Chem. Commun.*, 1270 (1990).

Type of reaction: elimination

Reaction condition: solvent-free

Keywords: methanethiol, [2+2]-cycloreversion, [1,2,(3)4]-elimination, melt reaction


Experimental procedures:

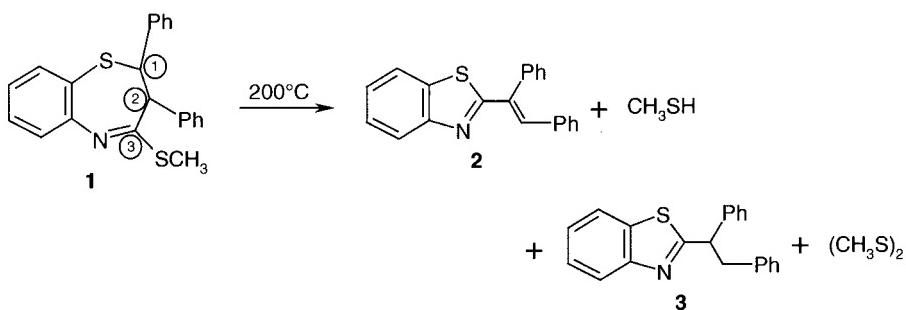
Compound **1** (150 mg, 0.41 mmol; from photolysis of stilbene with 2-methylmercapto-benzothiazole) was sealed under vacuum in a 10-mL Pyrex tube that was previously heated to red glow in order to remove adhering water. The whole tube was heated to 150 °C for 20 h in the dark. Separation by preparative HPLC (RP18, 80% methanol) gave 62 mg (82%) **4** and 25 mg (34%) **5** as well as 18 mg (14%) **2** and 2 mg (2%) **3**. **2** and **3** equilibrated in the melt at 150 °C to give a 8.0:1.0 ratio (6.1:1.0 at 200 °C when similarly prepared from **6**).

References: G. Kaupp, *Chem. Ber.*, **118**, 4271 (1985).

Type of reaction: elimination

Reaction condition: solvent-free

Keywords: benzothiazepine, [2,1,3]-elimination, methanethiol



Experimental procedure:

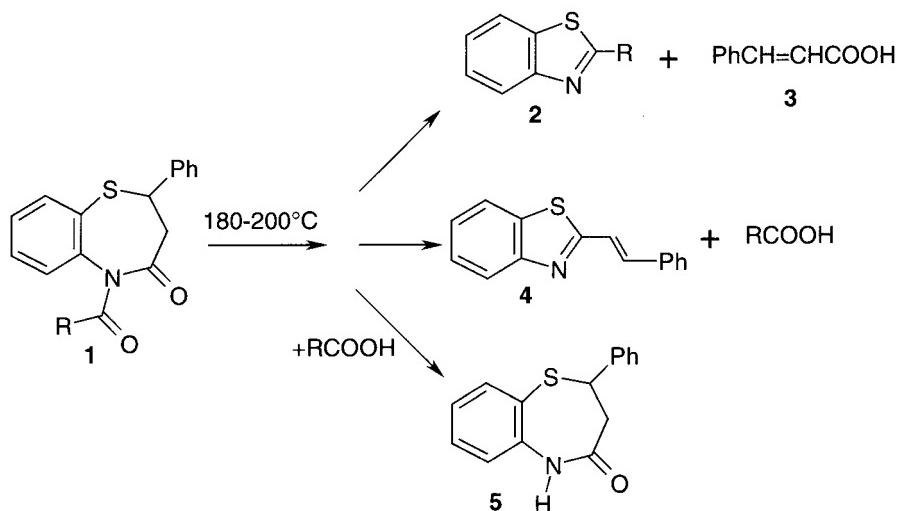
Compound **1** (500 mg, 1.39 mmol; from photolysis of stilbene and 2-methylmercapto-benzothiazole) was sealed under vacuum in a thick-walled Pyrex tube (the volume was about 100 mL) and heated to 200 °C for 20 h in the dark. Methanethiol (from the [2,1,3]-elimination) and dimethyldisulfide were condensed to a cold trap (-196 °C) at a vacuum line (65 mg, 97%). The residue was separated by preparative TLC on 200 g SiO₂ with benzene to give 340 mg (78%) of **2** (mp 108 °C, methanol) and 96 mg (22%) of **3**.

References: G. Kaupp, *Chem. Ber.*, **117**, 1643 (1984).

Type of reaction: elimination

Reaction condition: solvent-free

Keywords: benzothiazepinone, [1,5,5',(4)5]-elimination, ring contraction, complex elimination, benzothiazole



	R	T (°C)	t (h)	2 (%)	3 (%)	4 (%)	5 (%)
a	Me	200	5	35	27	40	12
b	Et	200	55	30	42	66	2
c	CH ₂ Ph	180	12	24	29	27	16
d	Ph	180	10	31	19	44	6

Experimental procedures:

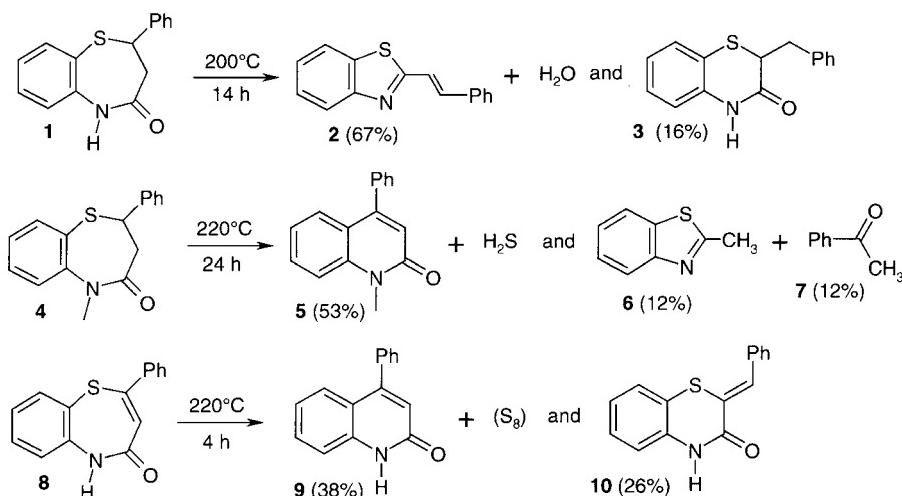
Compound **1a** (500 mg, 1.61 mmol) was heated to 200 °C for 5 h in an evacuated Pyrex ampoule. The raw material contained 46 mg (39%) propionic acid. The other products **2a**, **3**, **4**, **5** were separated by preparative TLC on 100 g SiO₂ with dichloromethane and obtained with the yields given. Similarly, **1b-d** gave **2b-d**, **3-5** and RCOOH.

References: G. Kaupp, D. Matthies, *Chem. Ber.*, **120**, 1741 (1987).

Type of reaction: elimination

Reaction condition: solvent-free

Keywords: benzothiazepinone, [2,1,3]-elimination, [1,2,3,2(3)]-elimination, [1,1]-elimination, [1,2/2,1]-rearrangement, benzothiazole, benzothiazinone, chinolin-2-one

**Experimental procedures:**

Compound **1** (1.00 g; 3.9 mmol) was sealed in an evacuated Pyrex tube and heated to 200±2 °C for 14 h. Preparative TLC on 200 g SiO₂ with dichloromethane (two developments) gave 625 mg (67%) **2** ([2,1,3]-elimination from the iminol tautomer) and 160 mg (16%) of the [1,2/2,1]-rearrangement product **3**.

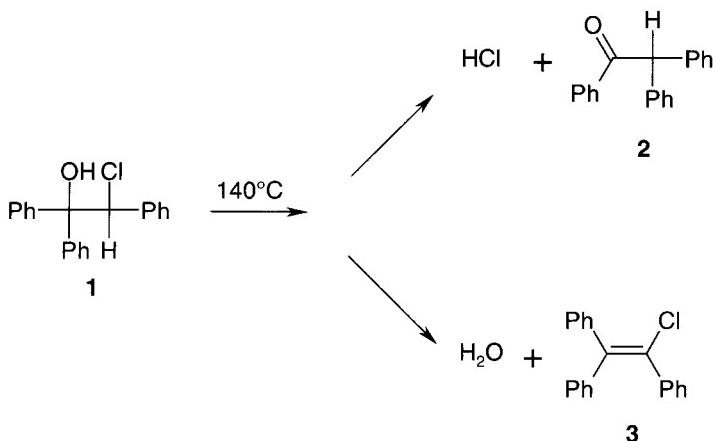
Similarly, compounds **4** and **8** were heated to 220 °C and the products of the [1,2,3,2(3)]-elimination **5**, of the [1,1]-elimination **9** and of the [1,2/2,1]-rearrangement **10** isolated by preparative TLC.

References: G. Kaupp, E. Gründken, D. Matthies, *Chem. Ber.*, **119**, 3109 (1986).

Type of reaction: elimination

Reaction condition: solvent-free

Keywords: chorohydrin, [1,2]-elimination, [1,2,3]-elimination, chlorotriphenylethen, diphenylmethyl phenyl ketone



Experimental procedure:

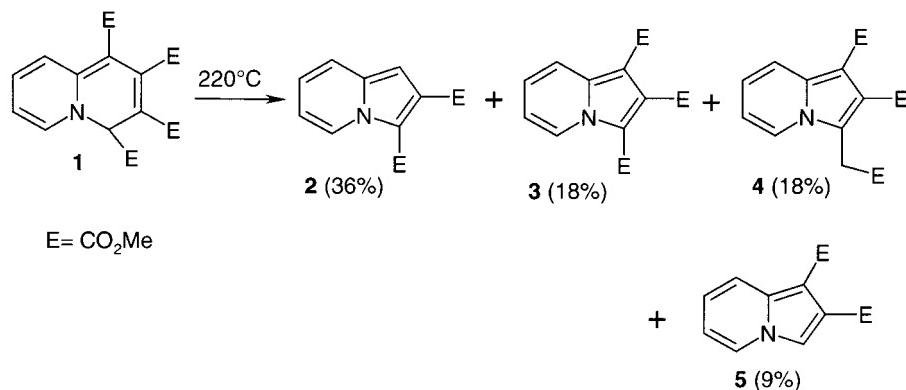
The chlorohydrin **1** (mp 138–139 °C, decomp.; 400 mg) was heated to 140 °C. It melted with decomposition to give **2** (by [1,2,3]-elimination) and **3** (by [1,2]-elimination) in a 66:34 ratio. The products were separated by preparative TLC on SiO_2 with dichloromethane.

References: G. Kaupp, D. Matthies, *Chem. Ber.*, **120**, 1897 (1987).

Type of reaction: elimination

Reaction condition: solvent-free

Keywords: quinolizine, complex elimination, ring contraction, indolizine



Experimental procedure:

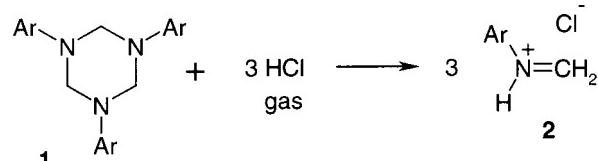
The quinolizine **1** (1.00 g, 2.75 mmol; from pyridine and dimethyl acetylenedicarboxylate) was heated to 220°C for 10 h in an evacuated sealed tube or in a V2A-autoclave. Gaseous and liquid products were CO₂, CO, MeOH, MeOMe, CH₃CO₂Me, OC(OMe)₂ and (MeO₂C)₂. The solid residue contained the indolizines **2**, **3**, **4** and **5** in the ratio 10:5:5:1. These were separated and isolated by preparative TLC on 400 g SiO₂ with benzene-methylacetate 3:2 (v/v).

References: G. Kaupp, D. Hunkler, I. Zimmermann, *Chem. Ber.*, **115**, 2467 (1982).

Type of reaction: elimination

Reaction condition: solid-state

Keywords: hexahydrotriazine, [2+2+2]-cycloreversion, waste-free, gas-solid reaction, *N*-arylmethylenimine hydrochloride



- a: Ar=phenyl
- b: Ar=4-tolyl
- c: Ar=4-anisyl

Experimental procedures:

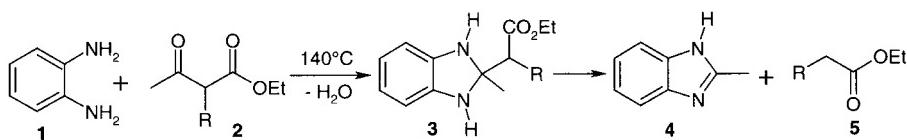
The hexahydrotriazines **1a–c** (3.00 mmol) were cooled to -18°C, -10°C and -10°C, respectively, in an evacuated 500-mL flask. HCl gas (500 mL, 1 bar) was let in through a vacuum line in 6 portions during 2 h or continuously through a stopcock in 3 h. Excess gas was evaporated after thawing to 4°C and 8 h rest. A yellow (**2a**), orange (**2b**), and brown (**2c**) solid was obtained with quantitative yield. The versatile iminium salts **2** are only stable in the solid state and should be used for aminomethylations soon after their preparation.

References: G. Kaupp, J. Schmeyers, J. Boy, *J. Prakt. Chem.*, **342**, 269 (2000).

Type of reaction: elimination

Reaction condition: solvent-free

Keywords: ethyl acetoacetate, *o*-phenylenediamine, acid cleavage, decarboxylation, carboxylic ester



	R	yield (%)
a:	H	45
b:	Me	79
c:	Et	68
d:	<i>i</i> Pr	61
e:	$\text{CH}_2\text{CH}=\text{CH}_2$	66
f:	COOEt	75
g:	CH_2COOEt	61
h:	$\text{CH}_2\text{CH}_2\text{COOEt}$	61
i:	CH_2Ph	67
j:	$\text{CH}_2\text{CH}_2\text{COOMe}$	65

Experimental procedures:

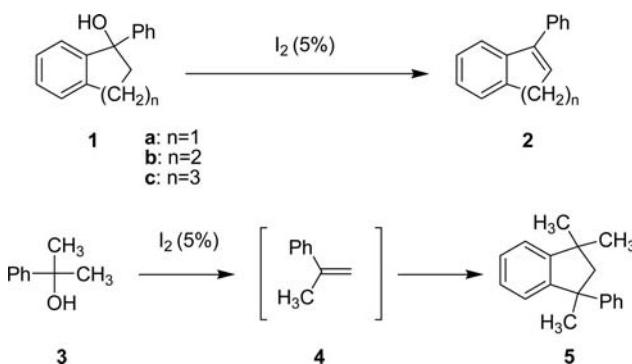
A mixture of 1,2-diaminobenzene **1** (0.20 mol) and α -substituted acetoacetate **2** (0.20 mol) was heated to 140°C for 4 h, when water, small quantities of the volatile esters **5** and small quantities of ethanol (from a side reaction) distilled over. In the cases **a–e** the distillation of the ester was completed by raising the temperature to a maximum of 220°C . Redistillation afforded the pure products **5a–e**. The esters **5f–i** were directly extracted from the cooled mixture with 4×60 mL CCl_4 . The tetrachloromethane solutions were extracted with water, the organic phase dried, evaporated and filtered over $\text{SiO}_2\text{-}60$ (400 g) with CH_2Cl_2 followed by distillation under vacuum. **5j** was extracted with CH_2Cl_2 (3×50 mL) after addition of 20 mL 15% HCl and purified by distillation. The solid 2-methylbenzimidazol **4** was isolated from the residues of distillation (**a–e**) and extraction (**f–j**) by treatment with CCl_4 and filtration.

References: G. Kaupp, H. Frey, G. Behmann, *Synthesis*, 555 (1985).

Type of reaction: elimination

Reaction condition: solvent-free

Keywords: iodine, dehydration, 1,1,3-trimethyl-3-phenylindane



Experimental procedures:

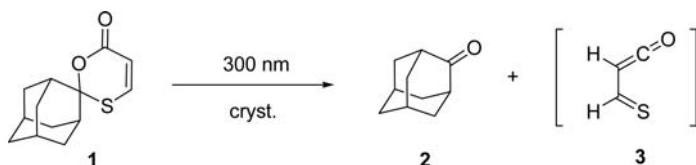
Alcohol **3** (solid) (1 mmol) and 5% of iodine (0.05 mmol, 12.7 mg) were triturated in a glass mortar for 1 min, transferred to a 15-mL flask and heated at 70 °C for 3 h. An aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ (10%, 20 mL) was then poured into the cooled mixture and the crude product was extracted with *tert*-butyl methyl ether (35 mL) and washed with water. Pure 1,1,3-trimethyl-3-phenylindane (**5**, colorless oil) was obtained by column chromatography (SiO_2 , hexane– CH_2Cl_2 4:1) in 91% yield.

References: G. Stavber, M. Zupan, S. Stavber, *Tetrahedron Lett.*, **47**, 8463 (2006).

Type of reaction: elimination

Reaction condition: solid-state

Keywords: adamantan-2-one, [4+2]cycloreversion



Experimental procedures:

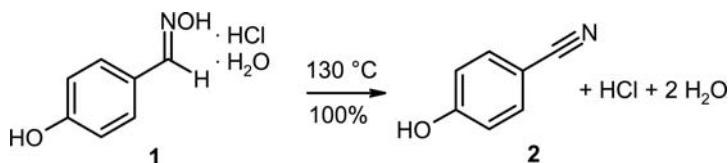
An Ar-degassed solution of **1** (118 mg, 0.5 mmol) in CH₂Cl₂ (5 mL) in a 25-mL tapered flask was slowly evaporated to produce a homogeneous solid film. After irradiation for 21 h, the originally colorless solid residue had turned yellowish. According to both GC and NMR analysis, the residue consisted of >90% **2**.

References: K. Schmidt, P. Margaretha, *Helvetica Chemica Acta*, **87**, 1906 (2004).

Type of reaction: elimination

Reaction condition: solvent-free

Keywords: thermolysis, oxime hydrochloride, nitrile

**Experimental procedure:**

The solid oxime hydrochloride hydrate **1** (150 mg, 0.78 mmol) was heated to 130 °C for 1 h in an open flask to obtain the pure nitrile **2** (93 mg, 0.78 mmol).

References: J. Mokhtari, M.R. Naimi-Jamal, H. Hamzeali, M.G. Dekamin, G. Kaupp, *ChemSusChem* (2008), submitted.

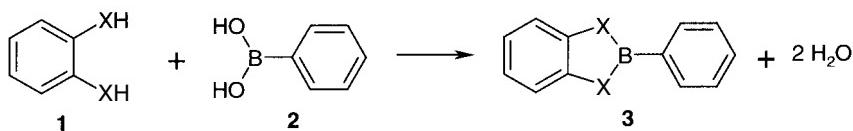
12 Protection

12.1 Solvent-Free Protection

Type of reaction: protection

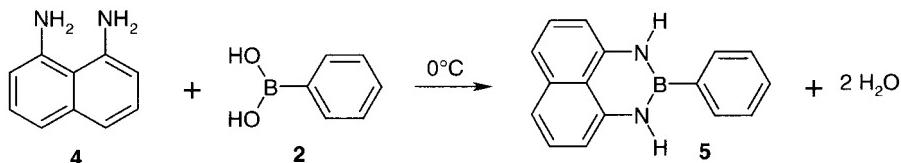
Reaction condition: solid-state

Keywords: phenylboronic acid, cyclization, phenylboronic ester



a: X=O (80 °C)

b: X=NH (40 °C)



Experimental procedures:

Compound 1 or 4 (1.00 mmol) and phenylboronic acid 2 (1.00 mmol) were co-ground in a mortar at room temperature or 0 °C and heated for 1 h to the temperature given. The pure products 3a–d or 5 were quantitatively obtained after drying in a vacuum at 80 °C.

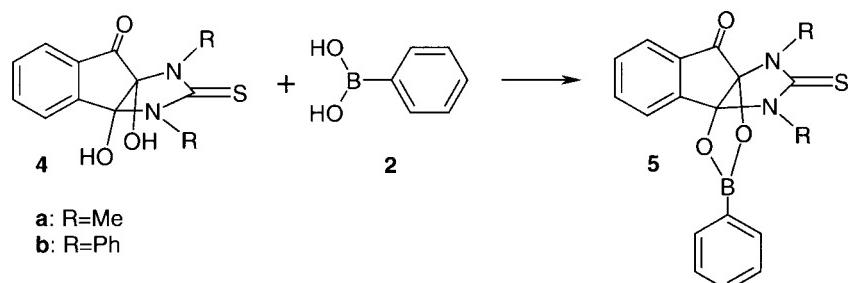
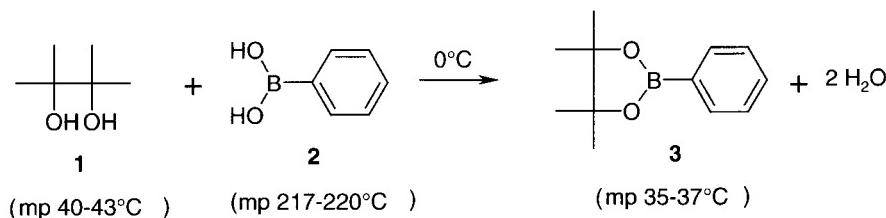
The compounds 1 or 4 can be recovered by heating in aqueous NaHCO₃ to 40 °C.

References: G. Kaupp, M.R. Naimi-Jamal, V. Stepanenko, *Chem. Eur. J.*, **9**, 4156 (2003).

Type of reaction: protection

Reaction condition: solid-state

Keywords: glycols, pinacol, phenylboronic acid, phenylboronic ester



Experimental procedures:

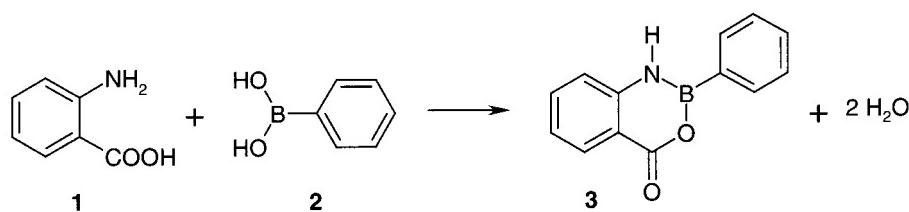
Pinacol **1** (1.00 mmol) and phenylboronic acid **2** were ball-milled at 0 °C for 1 h. The quantitatively obtained product **3** was dried in a vacuum. Mp 35–37 °C. Compound **5a, b** was quantitatively obtained if an equimolar mixture of **4a, b** and **2** was ball-milled at 50 °C for 1 h or if the co-ground mixture was heated to 140 °C for 1 h.

References: G. Kaupp, V.A. Stepanenko, M.R. Naimi-Jamal, *Chem. Eur. J.*, **9**, 4156 (2003).

Type of reaction: protection

Reaction condition: solid-state

Keywords: phenylboronic acid, anthranilic acid, cyclization



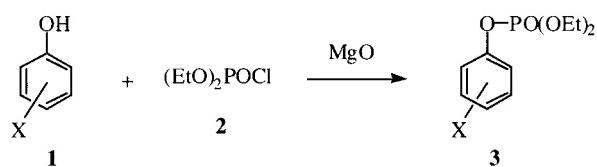
Experimental procedure:

Anthranilic acid **1** (274 mg, 2.00 mmol) and phenylboronic acid **2** (244 mg, 2.00 mmol) were ball-milled at room temperature for 1 h. The product **3** was quantitatively obtained after drying at 80 °C in a vacuum. Mp 223–224 °C.

References: G. Kaupp, V.A. Stepanenko, M.R. Naimi-Jamal, *Chem. Eur. J.*, **9**, 4156 (2003).

Type of reaction: protection**Reaction condition:** solvent-free

Keywords: phenol, diethyl chlorophosphonate, magnesia, phosphorylation, aryl diethyl phosphate

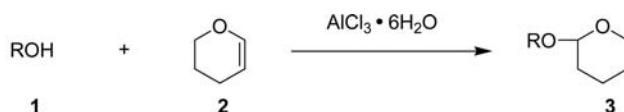


- | | |
|---|---|
| a: Ar=Ph | f: Ar=2,4-Cl ₂ C ₆ H ₃ |
| b: Ar=o-ClC ₆ H ₄ | g: Ar=m-MeC ₆ H ₄ |
| c: Ar=p-MeC ₆ H ₄ | h: Ar=o-NO ₂ C ₆ H ₄ |
| d: Ar=p-NO ₂ C ₆ H ₄ | i: Ar=α-C ₁₀ H ₇ |
| e: Ar=m-BtC ₆ H ₄ | j: Ar=β-C ₁₀ H ₇ |

Experimental procedures:

General Procedure for the Phosphorylation of Phenol with Diethyl Chlorophosphonate on the Surface of Magnesia. Magnesia (0.3 g) was added to a mixture of diethyl chlorophosphonate (0.86 mL, 6 mmol) and the phenol (5 mmol). This mixture was stirred at room temperature or 60 °C for 0.25–1 h. The solid mixture was washed with dichloromethane (4×25 mL). The solution was then washed with a dilute NaOH solution and a saturated sodium chloride solution and dried over MgSO₄. After evaporating of solvent, the crude product was isolated in a pure state by distillation in vacuo in 85–95% yield.

References: B. Kaboudin, *J. Chem. Res. (S)*, 402 (1999).

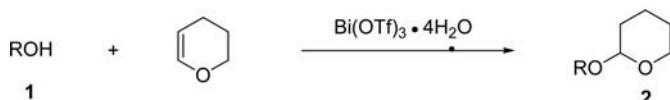
Type of reaction: protection**Reaction condition:** solvent-free**Keywords:** tetrahydropyranylation, alcohol, aluminum chloride hexahydrate

ROH : 1-Hexanol, 3-Hexanol, Cyclohexanol, Phenol, 4-Chlorophenol, 2-Naphthol
 Benzhydrol, *tert*-Butanol, Geraniol, Allyl alcohol, 3-Methyl-2-butene-1-ol
 1,2-Ethanediol, 1,4-Butanediol, 4-Chlorobenzyl alcohol

Experimental procedures:

Aluminum chloride hexahydrate (1 mmol), DHP (110 mmol) and benzyl alcohol (100 mmol) were mixed in a 50-mL round-bottomed flask and stirred at 30 °C; the progress of the reaction was monitored by TLC and GC-MS. The complete protection was ascertained by the disappearance of the alcohol signal in the GC. For solid substrates, moderate heating was required. The product was purified by filtering the reaction mixture through a short column of silica gel (2 cm length, 0.5 cm diameter) with petroleum ether (~4 mL) to obtain pure THP ether (99%).

References: V. V. Namboodiri, R. S. Varma, *Tetrahedron Lett.*, **43**, 1143 (2002).

Type of reaction: protection**Reaction condition:** solvent-free**Keywords:** tetrahydropyranyl ether, bismuth triflate**Experimental procedures:**

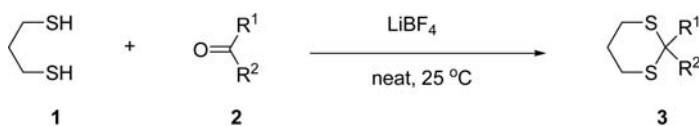
A solution of 1-pentanol (2.00 g, 22.7 mmol) and 3,4-dihydro-2H-pyran (2.69 mL, 29.50 mmol, 1.3 equiv.) was stirred in a flame-dried three-necked flask under N₂ as Bi(OTf)₃ · 4H₂O (14.9 mg, 0.023 mmol, 0.1 mol%) was added. The solution turned faint yellow and became slightly warm. After 3.5 h, the crude product was filtered through 60 g of basic alumina using ethyl acetate–hexane (15 : 85) as the eluent to afford 3.39 g (87%) of 1-pentanol THP ether as a colorless liquid. The product was characterized by IR, ¹H and ¹³C NMR spectroscopy.

References: J. R. Stephens, P. L. Butler, C. H. Clow, M. C. Oswald, R. C. Smith, R. S. Mohan, *Eur. J. Org. Chem.*, 3827 (2003).

Type of reaction: protection

Reaction condition: solvent-free

Keywords: 1,3-dithiane, lithium tetrafluoroborate



- | | |
|--|---|
| a: R ¹ = Ph; R ² = H | h: R ¹ = n-C ₇ H ₁₅ ; R ² = H |
| b: R ¹ = p-MeC ₆ H ₄ ; R ² = H | i: R ¹ = i-C ₃ H ₇ ; R ² = H |
| c: R ¹ = p-ClC ₆ H ₄ ; R ² = H | j: R ¹ = t-C ₄ H ₉ ; R ² = H |
| d: R ¹ = 2,4,6-Me ₃ C ₆ H ₂ ; R ² = H | k: R ¹ , R ² = -CH ₂ CH ₂ CH ₂ CH ₂ - |
| e: R ¹ = 2-furyl; R ² = H | l: R ¹ , R ² = -CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ - |
| f: R ¹ = PhCH=CH; R ² = H | m: R ¹ = Bu; R ² = Me |
| g: R ¹ = PrCH=CH; R ² = H | n: R ¹ = Ph; R ² = Me |

Experimental procedures:

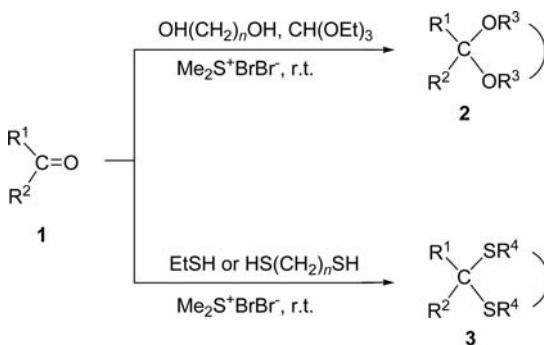
To a mixture of benzaldehyde (690 mg, 6.5 mmol) and LiBF₄ (46.9 mg, 0.5 mmol) 1,3-propanedithiol (541 mg, 5.0 mmol) was added dropwise with stirring over 10 min at 25 °C under N₂. After the reaction mixture was stirred at the same temperature for 1 h (completion of the reaction was checked by GC), it was directly distilled by using a Kugelrohr apparatus at 0.5 mmHg with an oven temperature of 170–200 °C to give 2-phenyl-1,3-dithian (982 mg, 100%) as a white solid.

References: K. Kazahaya, S. Tsuji, T. Sato, *Synlett*, 1640 (2004).

Type of reaction: Protection

Reaction condition: solvent-free

Keywords: acetalization, thioacetalization, (bromodimethyl)sulfonium bromide



- a: R¹=aryl/alkyl, R²=H/alkyl, R³=Me, -(CH₂)_n-, n=2,3

- b: R¹=aryl/alkyl, R²=H/alkyl/aryl, R⁴=Et, -(CH₂)_n-, n=2,3

Experimental procedures:

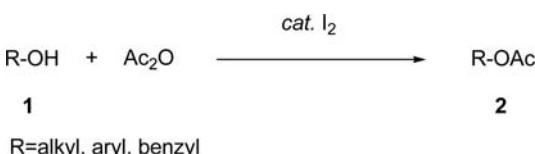
A catalytic amount of (bromodimethyl)sulfonium bromide (0.011 g, 0.05 mmol) was added to a mixture of the appropriate carbonyl compound (5 mmol), triethyl orthoformate (1 ml, 6 mmol) and 1,2-ethanediol (0.350 ml, 6 mmol) at room temperature and the mixture stirred until the starting material had disappeared, as monitored by TLC. After completion of the reaction, it was neutralized with NaHCO₃ solution and extracted with CH₂Cl₂ (2×25 mL), washed with water (2×15 mL) and dried with anhydrous Na₂SO₄. The organic extract was concentrated on a rotary evaporator and the crude residue was finally purified by alumina column chromatography or by distillation under reduced pressure to obtain the desired protected compound.

References: A. T. Khan, E. Mondal, S. Ghosh, S. Islam, *Eur. J. Org. Chem.*, 2002 (2004).

Type of reaction: protection

Reaction condition: solvent-free

Keywords: iodine, acetylation

**Experimental procedures:**

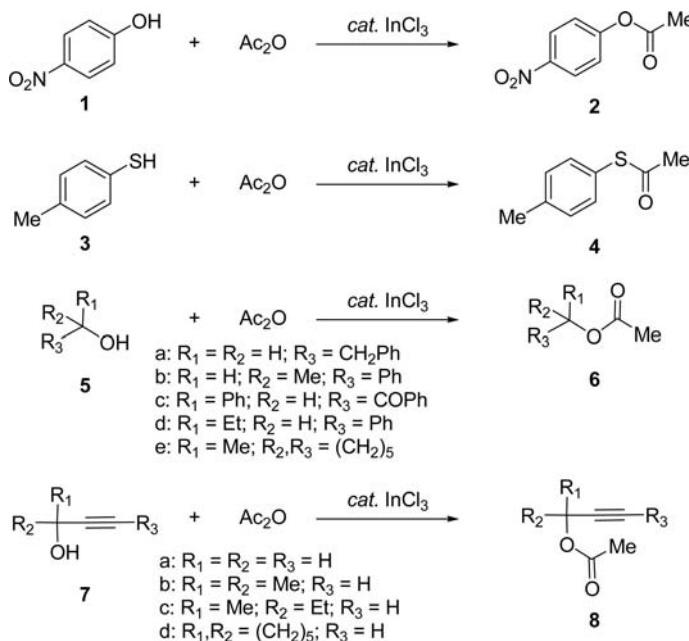
To a stirred mixture of the alcohol (1 mmol) and iodine (0.1 mmol), Ac₂O (1.05 mmol) was added and stirring continued at room temperature for the appropriate time (TLC). After completion of the reaction, iodine was destroyed by adding saturated sodium thiosulfate solution (5 mL). Diethyl ether (10 mL) was added and the phases were separated. The organic phase was washed with saturated NaHCO₃ solution (2×5 mL), brine (2×5 mL), dried (Na₂SO₄) and concentrated to give the pure product.

References: P. Phukan, *Tetrahedron Lett.*, **45**, 4785 (2004).

Type of reaction: protection

Reaction condition: solvent-free

Keywords: acylation, phenol, thiol, indium chloride



Experimental procedures:

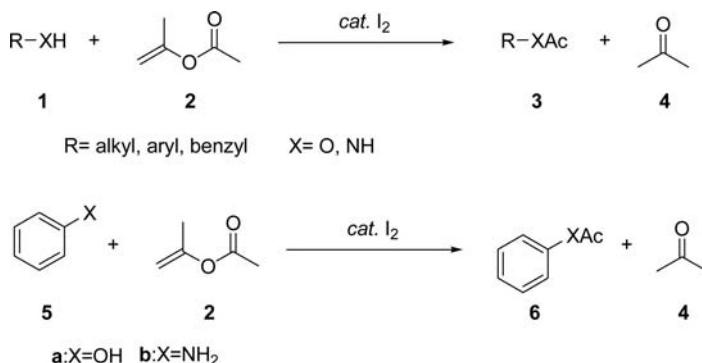
4-nitrophenol (347.5 mg, 2.5 mmol) was treated with Ac₂O (0.24 mL, 2.5 mmol) at room temperature for 30 min under magnetic stirring in the presence of InCl₃ (0.55 mg, 0.0025 mmol, 0.1 mol%). The reaction mixture was extracted with Et₂O to afford 4-nitrophenyl acetate (444 mg, 98%), which was in full agreement with the spectral data of an authentic sample.

References: A. K. Chakraborti, R. Gulhane, *Tetrahedron Lett.*, **44**, 6749 (2003).

Type of reaction: protection

Reaction condition: solvent-free

Keywords: iodine, isopropenyl acetate, acetylation

**Experimental procedures:**

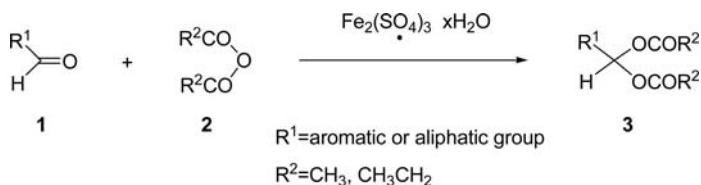
To a stirred mixture of alcohols, amines, phenols or acid (1 mmol) and isopropenyl acetate (IPA, 0.15 ml, 1.2 equiv.) at 85–90 °C was added iodine (5–10 mg, 0.02–0.04 mmol) with continued stirring at the same temperature for the indicated time. After completion of the reaction (TLC monitoring), the mixture was cooled to room temperature and the remaining iodine was destroyed by adding a 5% aqueous solution of sodium thiosulfate (2 mL). Diethyl ether (5–10 mL) was added and the phases were separated. The organic phase was washed with a saturated solution of NaHCO₃ (5 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. If necessary the product was purified by column chromatography on silica gel in hexane-ethyl acetate.

References: N. Ahmed, J.E. van Lier, *Tetrahedron Lett.*, **47**, 5345 (2006).

Type of reaction: protection

Reaction condition: solvent-free

Keywords: acylal, aldehyde, *gem*-dicarboxylate

**Experimental procedures:**

A mixture of benzaldehyde (10 mmol), freshly distilled acetic anhydride (12 mmol) and Fe₂(SO₄)₃ · xH₂O (0.20 mmol, 0.10 g) was stirred in a flask at ambient temperature. While stirring continued, the mixture solidified gradually. When the conversion was completed, as indicated by TLC, 1 mL CH₂Cl₂ was

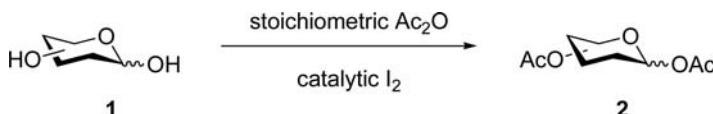
added to the mixture to dissolve the solid product. The catalyst was then collected by filtration and washed with CH_2Cl_2 (2×1 mL) for further use. The filtrate was concentrated under reduced pressure to give benzal diacetate as a white crystalline solid (2.02 g, 97%, mp 43–44 °C).

References: X. Zhang, L. Li, G. Zhang, *Green Chem.*, **5**, 646 (2003).

Type of reaction: protection

Reaction condition: solvent-free

Keywords: per-*O*-acetylated sugar, iodine



Experimental procedures:

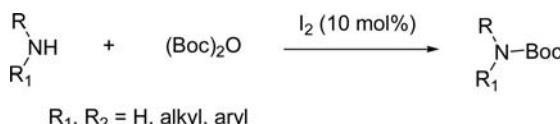
To a suspension of unprotected reducing sugar (10 mmol) in acetic anhydride (1.02 mol equiv. per hydroxy group) was added solid iodine (0.07 mmol) and the mixture was stirred at room temperature for 30 min–2 h, depending on the sugar. The reaction was monitored by TLC (2:1 n-hexane–ethyl acetate for monosaccharides, 1:1 for disaccharides). After completion of the reaction, the mixture was diluted with CH_2Cl_2 (20 mL), 10% aq. $\text{Na}_2\text{S}_2\text{O}_3$ solution (20 mL) was added and the mixture was stirred for 10 min. The organic extract was dried (Na_2SO_4) and concentrated, and the crude product was subjected to flash column chromatography using n-hexane–EtOAc as eluent (2:1 for monosaccharide derivatives and 1:1 for disaccharide derivatives) to afford the per-*O*-acetylated derivatives.

References: B. Mukhopadhyay, K. P. R. Kartha, D. A. Russell, R. A. Field, *J. Org. Chem.*, **69**, 7758 (2004).

Type of reaction: protection

Reaction condition: solvent-free

Keywords: *N*-Boc protection, amine, iodine



Experimental procedures:

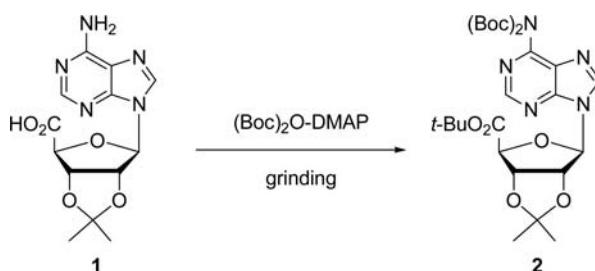
To a magnetically stirred mixture of amine (1 mmol) and $(\text{Boc})_2\text{O}$ (1 mmol) a catalytic amount of iodine (10 mol%) was added under solvent-free conditions at room temperature. After stirring the reaction mixture for the specified time, diethyl ether (10 mL) was added. The reaction mixture was washed with $\text{Na}_2\text{S}_2\text{O}_3$ (5%, 5 mL) and saturated NaHCO_3 and dried over Na_2SO_4 , the solvent was removed by a rotary evaporator under reduced pressure, and the residue was purified by silica gel column chromatography (60–120, 5–15% EtOAc in hexane) to afford the corresponding pure product.

References: R. Varala, S. Nuyula, S. R. Adapa, *J. Org. Chem.*, **71**, 8283 (2006).

Type of reaction: protection

Reaction condition: solvent-free

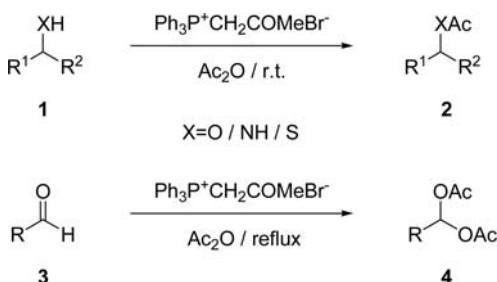
Keywords: *N*-protection, *O*-protection, Boc, ball-mill



Experimental procedures:

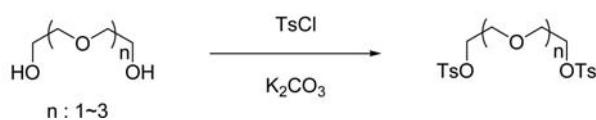
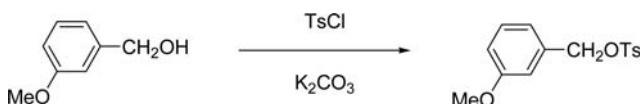
The nucleoside along with (Boc)₂O and catalyst DMAP (amounts as stated below) were placed in the ball mill with 9-mm Pyrex beads. For small scale reactions (ca. 100–300 mg) 16–20 beads were used; on gram-scale reactions as many as 25–30 were used. The mixture was ground (ca. 120–140 rpm) until the reaction was complete, as judged by TLC analysis of small aliquots scraped from the reactor and dissolved in a suitable solvent. On completion the thick oily product was washed from the apparatus using several small portions of a suitable solvent. The solvent was then evaporated and the residue was applied to a short column of silica gel.

References: S. A. Sikchi, P. G. Hultin, *J. Org. Chem.*, **71**, 5888 (2006).

Type of reaction: Protection**Reaction condition:** solvent-free**Keywords:** acylation, 1,1-diacylation, acetonyltriphenylphosphonium bromide**Experimental procedures:**

Acetonyltriphenylphosphonium bromide (0.05 mmol) was added to a mixture of the alcohol, or phenol, or amine or thiol (1 mmol) and acetic anhydride (1.5–2.0 mmol) and the mixture was stirred at room temperature for ca. 0.5–3.5 h. After complete disappearance of the starting material, as monitored by TLC, the mixture was quenched with a saturated hydrogencarbonate solution (2 mL). Finally, the reaction mixture was extracted with ethyl acetate ($20 \text{ mL} \times 3$). The combined organic extract was washed with water and dried over anhydrous sodium sulfate. After removal of the organic solvent in a rotary evaporator, the crude residue was passed through a silica gel column to isolate the desired pure acetate.

References: A.T. Khan, L.H. Choudhury, S. Ghosh, *Eur. J. Org. Chem.*, 2782 (2005).

Type of reaction: protection**Reaction condition:** solvent-free**Keywords:** alkyl tosylate, tosyl chloride/potassium carbonate

Experimental procedures:

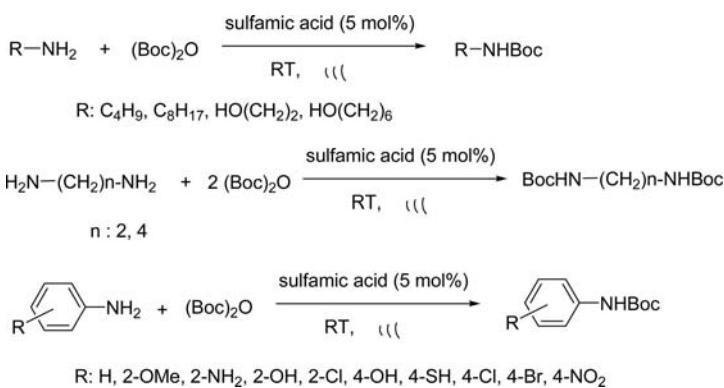
A mortar was charged with dry K_2CO_3 (50 g), diethylene glycol (9.47 mL, 100 mmol), and $TsCl$ (57.19 g, 300 mmol) which was ground vigorously for about 10 min. After the completion of tosylation, the remaining tosyl chloride was removed by the addition of powdered KOH (50 mmol) and the mixture was vigorously ground (2 min), the addition of a few drops of *t*-BuOH accelerated the disappearance of $TsCl$. The product was extracted by the addition of organic solvent. Further purification could be carried out on the crude solid tosylate by recrystallization from n-hexane. The yields were 89%.

References: F. Kazemi, A.R. Massah, M. Javaherian, *Tetrahedron*, **63**, 5083 (2007).

Type of reaction: protection

Reaction condition: solvent-free

Keywords: *N*-Boc protection, amine, sulfamic acid, sonication

**Experimental procedures:**

$(Boc)_2O$ (1.1 equiv.) and sulfamic acid (5 mol%) were mixed together neat in 10-mL round-bottomed flask at 25–28 °C. The amine (1 equiv.) was added and the resulting mixture was sonicated at room temperature in a US bath having a frequency of 33 KHz and an input power of 100 W. The flask was suspended in the center of the bath. The progress of the reaction was monitored by TLC analysis. The solid product was merely filtered off and washed with excess cold water. If the product was a liquid, its extraction was carried out using ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 . The solvent was distilled off under vacuum to yield the highly pure *N*-Boc derivative as an oil. In some cases, the purification was performed by column chromatography using silica gel (60–120 mesh) using petroleum ether–ethyl acetate (8:2) as an eluent.

References: D.J. Upadhyaya, A. Barge, R. Stefania, G. Cravotto, *Tetrahedron Lett.*, **48**, 8318 (2007).

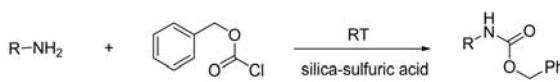
Type of reaction: protection

Reaction condition: solvent-free

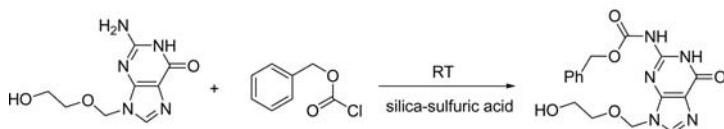
Keywords: *N*-benzyloxycarbonylation, silica–sulfuric acid



R: H, *p*-Cl, *p*-MeO, *o*-MeO, *p*-F, *p*-Me, *m*-CF₃



R: C₄H₉, C₆H₁₃, C₈H₁₇, PhCH₂



Experimental procedures:

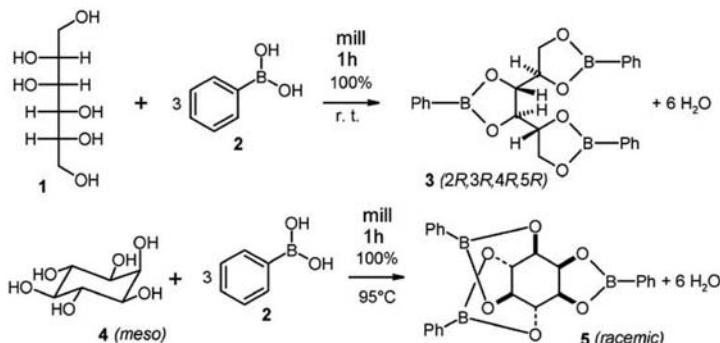
Amine (1 mmol) was added to benzylloxycarbonyl chloride (Cbz-Cl) (1.2 mmol) in the presence of silica–sulfuric acid (SSA, 10 wt% with respect to amine) and the reaction mixture was stirred under solvent-free conditions at room temperature for an appropriate time. After completion of the reaction, the product was extracted into ethyl acetate (3×20 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography to afford the corresponding *N*-benzyloxycarbonyl protected amines.

References: M. B. Gawande, V. Polshettiwar, R. S. Varma, R.V. Jayaram, *Tetrahedron Lett.*, **48**, 8170 (2007).

Type of reaction: protection

Reaction condition: solid-state

Keywords: phenylboronic acid, phenylboronic esters, mannitol, inositol, regioselectivity, stereospecificity, quantitative, solid-solid reaction, ball mill



Experimental procedures:

D-mannitol **1** (364 mg, 2.00 mmol) and **2** (732 mg, 6.00 mmol) were ball milled at 25 °C for 1 h and the solid nonsticky product dried at 80 °C *in vacuo*. (2R,3R,4R,5R)-**3** (880 mg, 100%) was regio- and obtained stereospecifically in pure form, mp 132–133 °C.

A mixture of *myo*-inositol **4** (360 mg, 2.00 mmol) and **2** (732 mg, 6.00 mmol) was ball-milled at 95 °C for 1 h. Pure nonsticky racemic **5** (875 mg, 100%) was obtained regiospecifically, mp 228–230 °C. Alternatively, the stoichiometric mixture of **4** and **2** was melted under high vacuum at 230 °C for 1 h in a 250-mL flask with the same result.

References: G. Kaupp, M.R. Naimi-Jamal, V. Stepanenko, *Eur. J. Chem.* **9**, 4156 (2003); G. Kaupp, Stereoselective thermal solid-state reactions, in: *Topics in Stereochemistry*, Vol. **25**, Wiley & Sons, Hoboken USA, 2006, Chapter 9, 303–354.

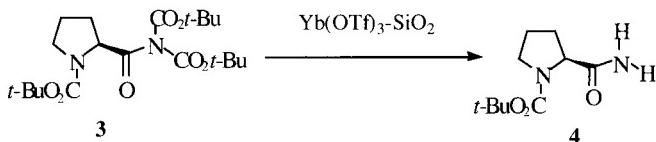
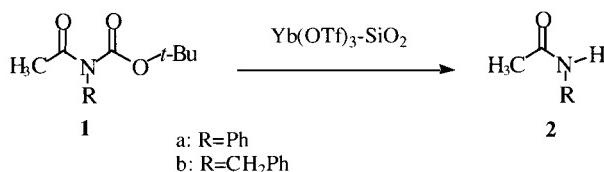
13 Deprotection

13.1 Solvent-Free Deprotection

Type of reaction: deprotection

Reaction condition: solvent-free

Keywords: *N*-*tert*-butoxycarbonyl group, Yb(OTf)₃, silica gel, amide



Experimental procedures:

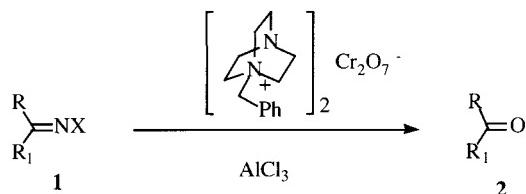
A mixture of the starting material (2 mmol) and 9% Yb(OTf)₃-SiO₂ (800 mg) was suspended in 2 mL of CH₂Cl₂ and the solvent was removed in vacuo. After standing at either room temperature or at 40 °C, the product was extracted into ethyl acetate. Concentration and purification by silica gel column chromatography or preparative TLC gave the corresponding free amide.

References: H. Kotsuki, T. Ohishi, T. Araki, K. Arimura, *Tetrahedron Lett.*, **39**, 4869 (1998).

Type of reaction: deprotection

Reaction condition: solvent-free

Keywords: oximes, semicabazone, 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane, dichromate, aldehyde, ketone



a: X=OH; R=H; R₁=5-Me-furyl

b: X=OH; R=H, R₁=3,4-MeO₂C₆H₃

c: X=OH; R=Me; R₁=4-BrC₆H₄

d: X=OH; R=Me; R₁=4-ClC₆H₄

e: X=OH; R=CH₂Br; R₁=4-BrC₆H₄

f: X=OH; R,R₁=-(CH₂)₄-

g: X=OH; R,R₁=-(CH₂)₅-

h: X=OH; R=Me; R₁=Ph

i: X=OH; R=R₁=Ph

j: X=NHC(=O)H₂; R=H; R₁=5-Me-furyl

k: X=NHC(=O)H₂; R=H, R₁=2,5-MeO₂C₆H₃

l: X=NHC(=O)H₂; R=Me; R₁=4-BrC₆H₄

m: X=NHC(=O)H₂; R=Me; R₁=3-ClC₆H₄

n: X=NHC(=O)H₂; R=CH₂Br; R₁=4-BrC₆H₄

o: X=NHC(=O)H₂; R=Me; R₁=3-MeOC₆H₄

p: X=NHC(=O)H₂; R=Me; R₁=3-NO₂C₆H₄

R 4

Experimental procedures:

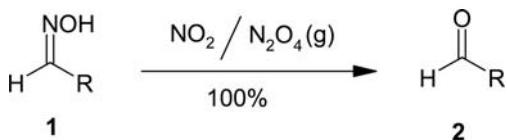
A mixture of benzophenone oxime (0.16 g, 0.803 mmol), 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane dichromate (0.50 g, 0.803 mmol), and aluminum chloride (11 mg, 0.08 mmol) was crushed with a mortar and pestle for 35 s until TLC showed complete disappearance of starting oximes. CCl₄ (10 mL) was added to the reaction mixture and, after vigorous stirring, the mixture was filtered off. The solvent was evaporated by rotary evaporator to give pure benzophenone (0.129 g, 88%).

References: A.R. Hajipour, S.E. Mallakpour, I. Mohammadpoor-Baltork, S. Khoei, *Synth. Commun.*, **31**, 1187 (2001).

Type of reaction: deprotection

Reaction condition: solid state

Keywords: gas-solid reaction, liquid-solid reaction, oximes, nitrogen dioxide



- a: R = 4-ClC₆H₄; -4°C; 3 min
- b: R = 2-NO₂C₆H₄; -8°C; 3 min
- c: R = 3-NO₂C₆H₄; -5°C; 1.5 min
- d: R = 4-NO₂C₆H₄; -5°C; 2 min
- e: R = 4-CNC₆H₄; 0°C; 6 min
- f: R = 4-(NMe₂)C₆H₄; 0°C; 3 min
- g: R = 4-MeC₆H₄; 20°C; 2 min
- h: R = 4-MeOC₆H₄; 20°C; 3 min
- i: R = CHMe₂; 20°C; 2 min

Experimental procedures:

The oxime **1** (1.00 mmol) in an evacuated 100-mL flask at the temperature given (chosen as low as necessary to completely suppress any oxidation to the corresponding acids) was exposed to gaseous NO_2 (0.6 bar, >2.7 mmol). The reactive gas partly liquefied initially in the low-temperature experiments **a–f**. The mixture was allowed to react for the specified time. After condensation of the gases of reaction to a trap at 77 K diethyl ether (4 mL) was added. The organic phase was washed with water, dried over Na_2SO_4 , concentrated, and evaporated in a good vacuum to give the pure aldehyde **2**.

The N_2O_3 and N_2O_4 condensates in the cold trap were treated with dry air at -30 to -20 °C for complete oxidative recovery of solid N_2O_4 for further use as gaseous NO_2 .

References: J. Mokhtari, M.R. Naimi-Jamal, H. Hamzeali, M.G. Dekamin, G. Kaupp, *ChemSusChem* (2008), submitted.

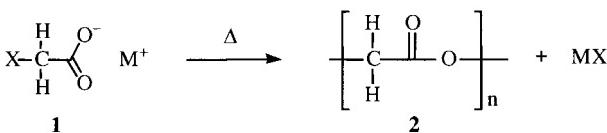
14 Polymerization

14.1 Solvent-Free Polymerization

Type of reaction: C–O bond formation

Reaction condition: solid-state

Keywords: halogenoacetate, polymerization, polyglycolide



a: M=Na; X=Cl

b: M=K; X=Cl

c: M=NH₄; X=Cl

d: M=Ag; X=Cl

e: M=0.5 Ca²⁺; X=Cl

f: M=Na; X=Br

g: M=Ag; X=Br

h: M=Na; X=I

i: M=K; X=I

Experimental procedures:

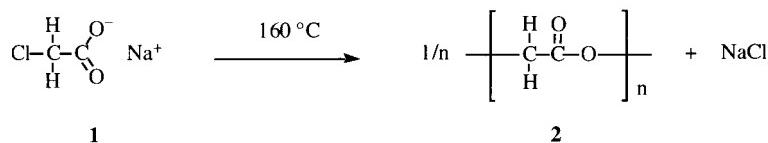
Ca. 5–20 g of mortared halogenoacetate **1** was annealed in a round-bottom flask in an oil bath. The sample should be heated carefully to avoid self-heating that may lead to combustion. Reaction conditions: Sodium chloroacetate: 60 min at 180 °C; potassium chloroacetate: 60 min at 150 °C; ammonium chloroacetate: 30 min at 110 °C; silver chloroacetate: 60 min at 180 °C; sodium bromoacetate: 60 min at 160 °C; silver bromoacetate: 10 min at 100 °C; potassium iodoacetate: 60 min at 180 °C. The sample changed from a white to a yellow or grayish powder but retained its morphology, except ammonium chloroacetate. The polyglycolide **2** was separated from the also formed metal halide by multiple washing with water. Yield: quantitative. Polyglycolide: White powder, insoluble in common solvents, partially soluble in 1,1,1,3,3-hexafluoro-2-propanol.

References: M. Epple, H. Krischnick, *Chem. Ber.*, **129**, 1123 (1996).

Type of reaction: C–O bond formation

Reaction condition: solid-state

Keywords: chlorocarboxylic acid, oligomerization, polymerization, polyglycolide

**Experimental procedures:**

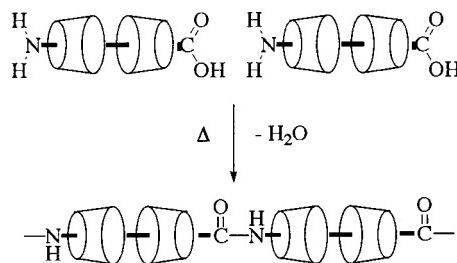
Ca. 5 g of ground halogenocarboxylate **1** is heated in an open round-bottom flask in an oil bath. Heating to the reaction temperatures should occur carefully; otherwise, decomposition and combustion may occur. Reaction conditions: sodium 2-chloropropionate **1**: 30 min at 160°C; sodium 3-chloropropionate **2**: 45 min at 120°C; sodium 2-chlorobutyrate **3**: 30 min at 160°C. The reaction mixture becomes liquid during the reaction. After reaction is complete, a viscous brown-yellow oil remains. The organic part of the reaction mixture is extracted with CHCl₃, and the undissolved NaCl is filtered off. Removal of CHCl₃ in vacuo leaves a viscous yellow oil.

References: M. Epple, H. Kirshenick, *Liebigs Ann.*, 81 (1997).

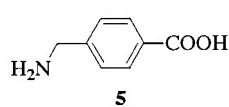
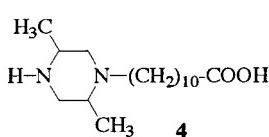
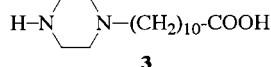
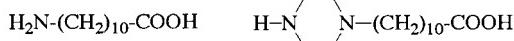
Type of reaction: C–N bond formation

Reaction condition: solid state

Keywords: ω -amino carboxylic acid, cyclodextrins, host-guest chemistry, condensation, polyamides



 : α -cyclodextrin
1a



Experimental procedures:

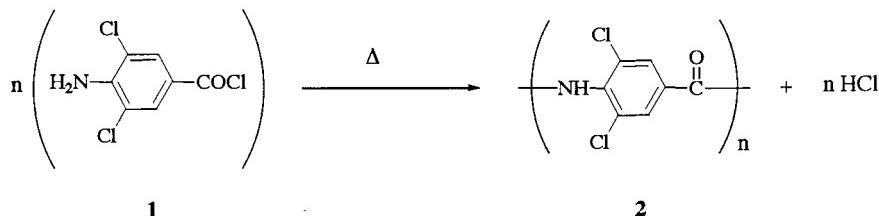
$[2 \cdot (1\mathbf{a})_2]$ (203 mg) was tempered at 230 °C and 0.1 mbar for 5 h. Yield: 196 mg (97.4%). $[2 \cdot (1\mathbf{a})_2]_n$ (1.172 g) was stirred in 1% HCl (60 mL) at 80 °C for 25 h. The resulting precipitate was filtered and washed several times with water and methanol. Yield: 103.1 mg (93.9%). For the molecular mass determination, $(2)_n$ (90 mg, 0.49 mmol) was added to absolute CH_2Cl_2 (15 mL) and stirred with trifluoroacetic anhydride (0.21 g, 1.0 mmol) at 25 °C for 24 h. After removal of the solvent by distillation, the residue was dried at 0.1 mbar. Yield: 139 mg (96%) *N*-trifluoroacrylated nylon-11. The soluble product was subjected to size exclusion chromatography on Styragel column (Waters, calibration with polystyrene standards) in absolute THF.

References: M. B. Steinbrunn, G. Wenz, *Angew. Chem. Int. Ed. Engl.*, **35**, 2139 (1996).

Type of reaction: C–N bond formation

Reaction condition: solid-state

Keywords: 3,5-dihalo-4-aminobenzoylchloride, polymerization, polyamide

**Experimental procedures:**

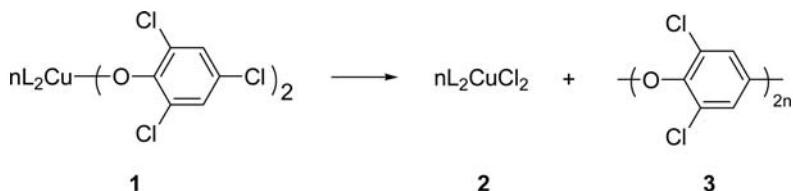
The crystalline solid was placed in a 1-cm test tube equipped with a side arm. The test tube was heated in a bath of silicone oil and maintained at a constant temperature under dry nitrogen. Depending on the particular experiment the temperature was kept between 95 and 300 °C. The contents of the tube became opaque but did not melt. The solid polymer retained the habit of the monomer crystals. The reaction could be followed by changes in infrared spectra.

References: R. B. Sandor, B. M. Foxman, *Tetrahedron*, **56**, 6805 (2000).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: poly(dihalophenylene oxide), bis (4-chloro-2,6-dibromo phenoxo) ethylenediamine copper (II) complex

**Experimental procedures:**

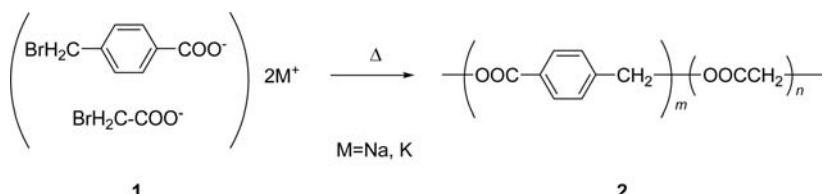
Poly(dihalophenylene oxide)s were synthesized by thermal decomposition of complexes (2 g) at constant temperature (70–250 °C) for a period of time over the range 3–48 h. The resulting solid was dissolved in a minimum amount of toluene, then poured into a large excess of methanol containing a few drops of HCl.

References: O. Sanli, M. Pulat, D. Kisakürek, *Eur. Polym. J.*, **31**, 1255 (1995).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: alkali 4-(bromomethyl)benzoate-bromoacetate, copolycondensation

**Experimental procedures:**

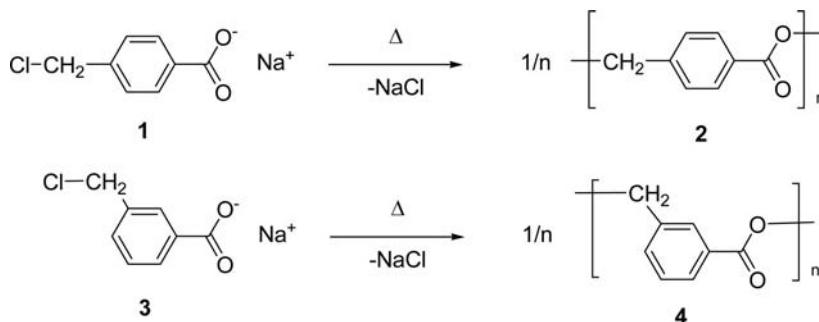
The appropriate monomeric binary salt (1.0 g) was placed in a Pyrex tube, dried under reduced pressure for 1 h prior to reaction and heated in an oil bath under reduced pressure at 150–200 °C for 2 h. The product was dissolved in a mixed solvent of 1,1,2,2-tetrachloroethane–phenol (40/60 by weight) or in DMSO, filtered through a glass filter to remove alkali bromides and poured into methanol to initiate precipitation. The resulting precipitate was washed with methanol and dried under reduced pressure. The product was purified by reprecipitation.

References: M. Inoki, F. Akutsu, F. Fang, E. Mitsui, Y. Kasashima, K. Naruchi, *J. Chem. Soc. Perkin Trans. 2*, 2257 (1997).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: halogenomethylbenzoate, poly(hydroxymethylbenzoic acid)



Experimental procedures:

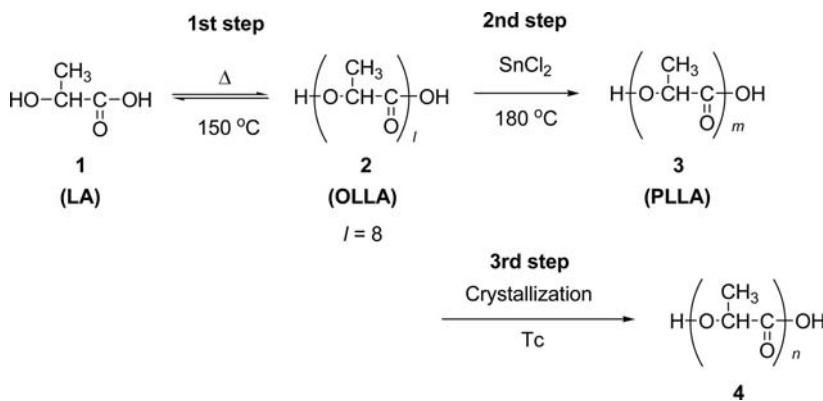
Polymerization on a preparative scale was carried out in a round-bottom flask heated in an oil bath under vacuum (ca. 1 mbar). The typical sample mass was 1 to 5 g. The polymerization was carried out for 0.5 to 24 h near the onset temperature determined from DSC experiments. In most isothermal experiments, no liquefaction was observed, therefore a solid-state polymerization appears likely.

References: O. Herzberg, M. Epple, *Macromol. Chem. Phys.*, **200**, 2662 (1999); O. Herzberg, H. Ehrenberg, S.J. Kitchin, K.D.M. Harris, M. Epple, *J. Solid State Chem.*, **156**, 61 (2001).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: polycondensation, L-lactic acid, poly(L-lactic acid)



Experimental procedures:

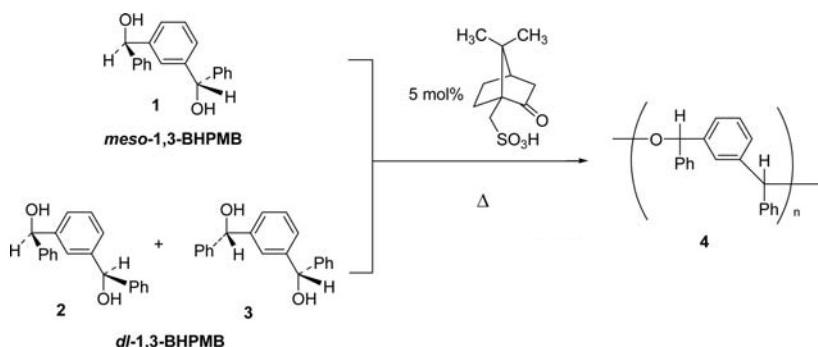
LA was dehydrated into oligo(L-lactic acid) (OLLA) whose degree of polymerization (DP) was 8.0 on average. It was mixed with tin(II) chloride hydrate (SnCl_2) (0.4 wt% relative to OLLA) and *p*-toluenesulfonic acid (TSA) (an equimolar ratio to SnCl_2). The mixture was then heated to 180 °C under mechanical stirring. The pressure of the reaction system was reduced stepwise to 10 Torr in 1 h, at which pressure the reaction was continued for 5 h. At the end of this reaction, the product was cooled to form a white solid. It was then crushed into granules and evenly divided between four test tubes. Each tube was preheated at 105 °C for 1 or 2 h *in vacuo*. During this preheating, the product was crystallized and became resistive to fusion, even when heated at a higher temperature. The solid-state post-polycondensation was continued at 150 °C at 0.5 Torr. At 10 h intervals, each of the tubes was opened and the product was subjected to various analyses in its as-formed state.

References: S.-I. Moon, C.-W. Lee, I. Taniguchi, M. Miyamoto, Y. Kimura, *Polymer*, **42**, 5059 (2001).

Type of reaction: Polymerization

Reaction condition: solvent-free

Keywords: 1,3-bis(hydroxyphenylmethyl)benzene

**Experimental procedures:**

1,3-BHPMB was ground with 5 mol% (1*S*)-10-camphorsulfonic acid (CSA) in an agate mortar and pestle. The mixture was heated in a tube under a nitrogen flow. To monitor the polymerization, a small aliquot sampled from the reaction mixture was subjected to the following work-up before GPC analysis. A saturated aqueous NaHCO_3 solution was added to an aliquot, and the mixture then underwent extraction with chloroform. The organic layer was dried over anhydrous MgSO_4 , and the solvent was removed *in vacuo*. The residue was subjected to GPC analysis. To isolate the product polymer, this residue was dissolved in a small amount of chloro-

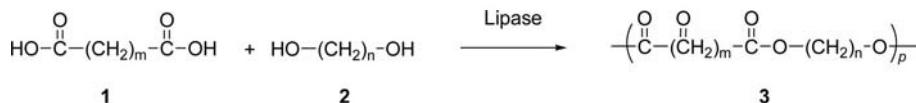
form and then added dropwise to a large amount of diethyl ether. The precipitated polymer was collected by centrifugation and dried *in vacuo*.

References: M. Suzuki, T. Sasaki, G. Matsuura, M. Kimura, *J. Polym. Science; Part A, Poly. Chem.*, **41**, 3564 (2003).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: enzymatic polymerization, dicarboxylic acid, polyester



Experimental procedures:

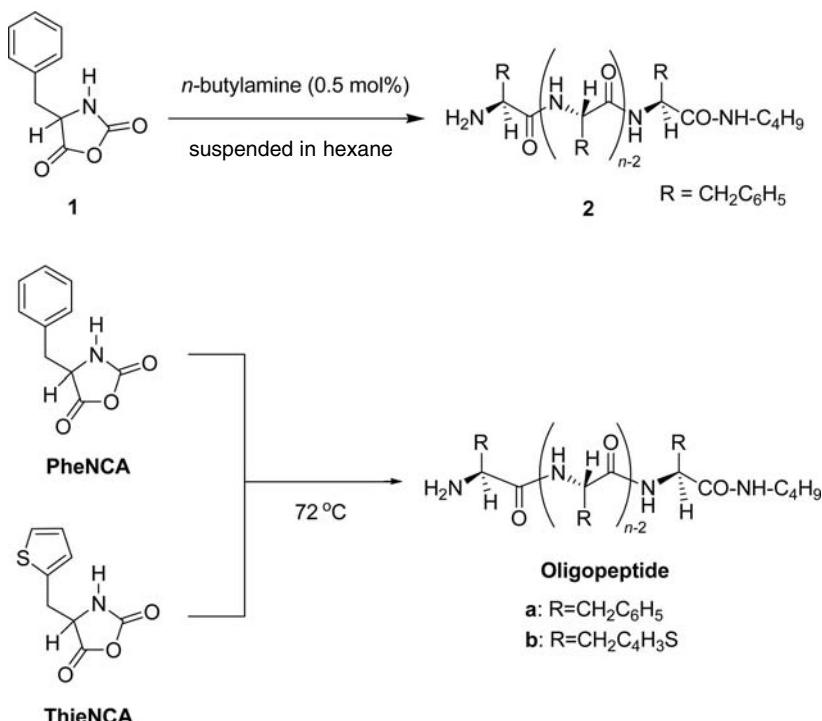
A mixture of sebacic acid (0.41 g, 2.0 mmol), 1,4-butanediol (0.18 g), and lipase CA (0.10 g) was placed in a dried tube under argon and sealed. The tube was kept under gentle stirring at 60°C for 8 h. A small amount of chloroform was added to the mixture and part of the organic solution was separated by filtration. The filtrate was poured into a large amount of methanol. The resulting precipitates were collected by centrifugation, followed by drying *in vacuo* to give the polymer (0.29 g, 56%).

References: H. Uyama, K. Inada, S. Kobayashi, *Chem. Lett.*, 1285 (1998).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: phenylalanine-*N*-carboxyanhydride, topochemical reaction



Experimental procedures:

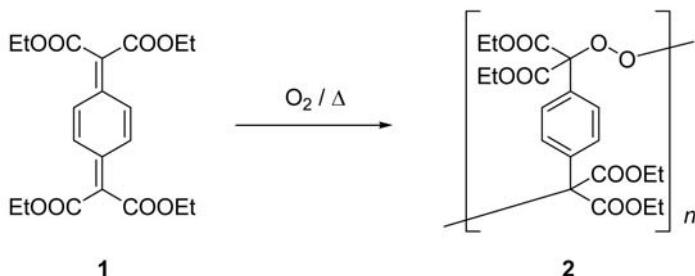
Solid-state polymerization was performed (under an argon atmosphere) in crystals suspended in hexane, using *n*-butylamine (0.5 mol%) as an initiator, for 12 and 72 h at 50 and 22 °C, respectively. The gel-like product was poly(L-lactic acid) washed with dry THF and ethyl acetate until all the monomer was removed, as confirmed by infrared spectroscopy. The product in its final form was centrifuged and dried.

References: J. G. Nery, G. Bolbach, I. Weissbuch, M. Lahav, *Angew. Chem. Int. Ed.*, **42**, 2157 (2003); J. G. Nery, G. Bolbach, I. Weissbuch, M. Lahav, *Chem. Eur. J.*, **11**, 3039 (2005).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: tetrakis(ethoxycarbonyl)quinodimethane, molecular oxygen

**Experimental procedures:**

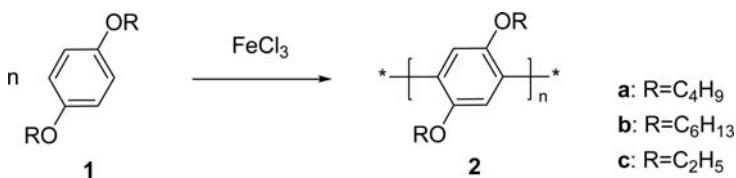
A given amount of **1** was put in a Pyrex ampoule, which was sealed either without degassing (in air) or with degassing under reduced pressure (*in vacuo*). Thermal polymerization was carried out by putting the ampoule in an oil bath at 35 or 60 °C for a given time. The conversion was determined by removing an aliquot from the reaction system after a certain reaction time, dissolving it in CDCl₃, and recording the ¹H NMR spectrum. The conversion was calculated from the ratio of the peak area at δ=7.45 ppm due to the quinonoid structure of **1** to that at δ=7.53 ppm due to the phenylene group of the polymer.

References: S. Nomura, T. Itoh, M. Ohtake, T. Uno, M. Kubo, A. Kajiwara, K. Sada, M. Miyata, *Angew. Chem. Int. Ed.*, **42**, 5468 (2003); S. Nomura, T. Itoh, H. Nakasho, T. Uno, M. Kubo, K. Sada, K. Inoue, M. Miyata, *J. Am. Chem. Soc.*, **126**, 2035 (2004).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: poly(*p*-alkoxyphenylene)s, 1,4-di-*n*-butoxybenzene

**Experimental procedures:**

1,4-Di-*n*-butoxybenzene (0.61 g, 3 mmol) and anhydrous FeCl₃ powder (1.50 g, 9 mmol) were added to a mortar. After grinding for 20 to 30 min with a glass pestle, the mixture was put into ethanol (100 ml) containing 5% hydrochloric acid and then stirred for 5 min. The precipitated polymer was collected by filtration, washed with ethanol until the solution looked colorless, and dried in an oven at 50 °C. The polymer was then extracted with alcohol using a Soxhlet ex-

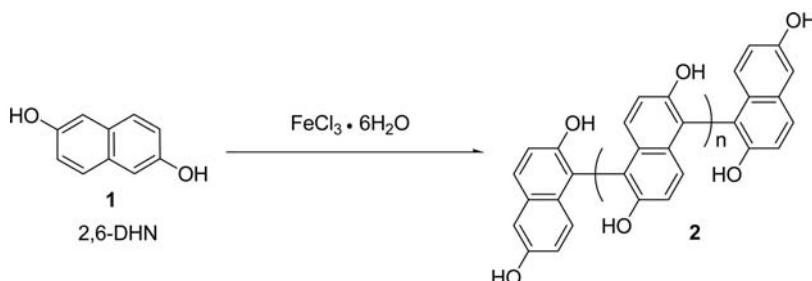
tractor for 24 h and dried overnight in an oven at 50 °C. The final product was a light brown solid (0.51 g, 83%).

References: W. B. Bai, C. M. Zhan, *Chem. Lett.*, **34**, 924 (2005).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: oxidative-coupling, 2,6-dihydroxynaphthalene



Experimental procedures:

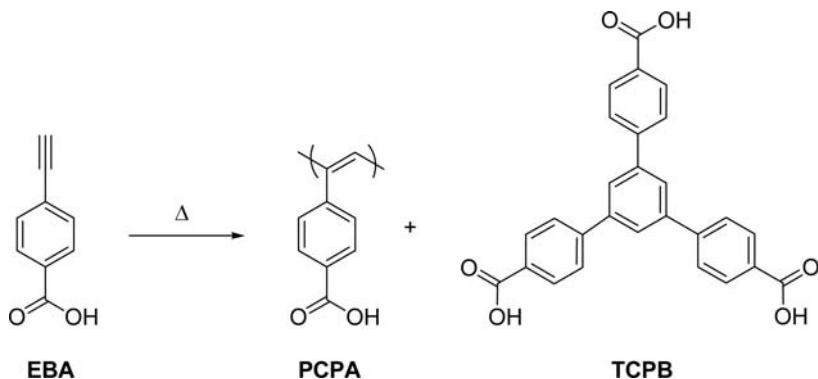
Crystalline 2,6-DHN **1** (or its amine-complex) and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (300 mol% for 2,6-DHN) were mixed well with an agate mortar and pestle. The black mixture was kept at room temperature or heated at 50 °C, and the reaction was monitored by TLC. An aqueous Na_2SO_3 solution was added to stop the reaction. The precipitate, poly(2,6-dihydroxy-1,5-naphthylene) **2**, was washed several times with 1 M aqueous HCl and then water. The dark green polymer obtained was dried under vacuum and subjected to acetylation without further purification.

References: M. Suzuki, Y. Yatsugi, *Chem. Commun.*, 162 (2002).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: *p*-ethynylbenzoic acid, poly(phenylacetylene)



Experimental procedures:

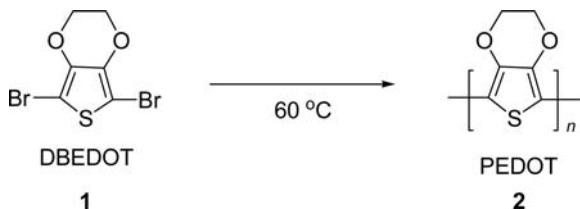
Powdered crystals of EBA (200 mg) were placed in a 100-mL round-bottomed flask and heated in an oil bath at 115°C (A), and at 125°C (B), under N₂ for 3 days. The dark reddish-brown colored products were then extracted for 3 days in a Soxhlet extractor using toluene to remove the unreacted monomer. The products were vacuum dried at ~60°C for 7–10 days yielding (A: 34%, B: 42%) red (A) and orange (B) powders entirely free of monomer and toluene. NMR and GPC analysis of the thermal products indicated that A consisted of pure PCPA, whereas B consisted of a near-equal mixture of TCPB and PCPA.

References: J.M. Njus, D.J. Sandman, L. Yang, B.M. Foxman, *Macromolecules*, **38**, 7645 (2005).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: poly(ethylenedioxythiophene), 2,5-dibromo-3,4-ethyleneioxythiophene



Experimental procedures:

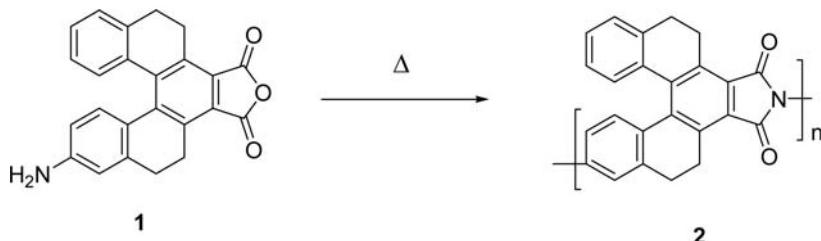
DBEDOT (0.01–2 g) was incubated at 60 °C for 24 h and dried *in vacuo* (0.1 mbar) at room temperature to give black crystals of bromine-doped PEDOT.

References: H. Meng, D. F. Perepichka, F. Wudl, *Angew. Chem. Int. Ed.*, **42**, 658 (2003).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: 3-amino-5,6,9,10-tetrahydro[5]-helicene-7,8-dicarboxylic anhydride



Experimental procedures:

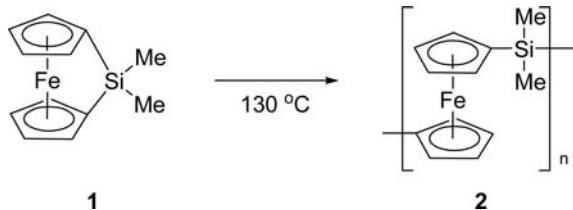
Oligoimides of **2** are produced after treatment of monomer **1** at 350 °C in the solid state. Oligoimides of **2** were prepared by time-controlled polymerization and fractionated from chloroform-methanol.

References: T. P. Bender, Z. Y. Wang, *Macromolecules*, **33**, 9477 (2000).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: ferrocenyldimethylsilane, poly(ferrocenyldimethylsilane)



Experimental procedures:

Heating of the monomer (1.0 g, mp 78 °C) at 130 °C for 10 min *in vacuo* produced molten polymer in the first instance and then, following a steady increase in viscosity, a solid substance, confirmed by GPC and ¹H NMR analysis to be the polymer, poly(ferrocenyldimethylsilane). Following further heating for a period of 30 min, the polymeric product was purified by dissolving in THF (40 mL), concentrating this solution to approximately 10 mL and then precipitating the polymer by adding the solution in THF to an excess (300 mL) of hexane. The precipitate was filtered, redissolved in toluene, filtered through a membrane of pore size 0.2 m, concentrated to 10 mL (a solution of approximately 1%) and then either precipitated in acetone or set as a film.

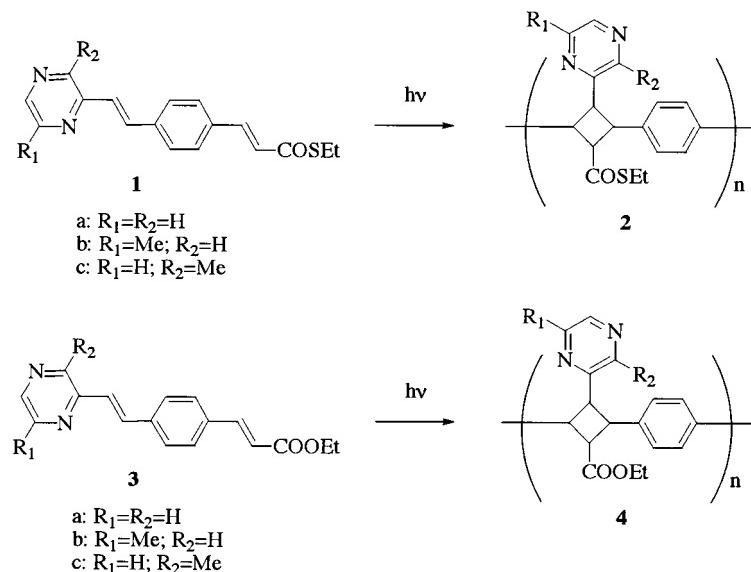
References: J. Rasburn, R. Petersen, T. Jahr, R. Rulkens, I. Manners, G.J. Vancso, *Chem. Mater.*, **7**, 871 (1995).

14.2 Solvent-Free Polymerization under Photoirradiation

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: ethyl 4-[2-(2-pyrazinyl)ethenyl]cinnamate, photopolymerization, cyclobutane



Experimental procedures:

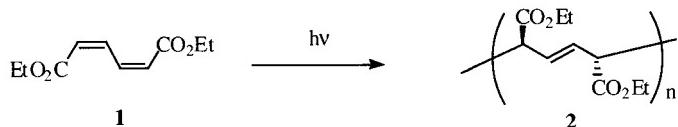
Finely powdered crystals (100 mg) were dispersed in 300 mL of water containing a few drops of a surfactant (Nikkol TL-10FF) and irradiated with a 100-W high-pressure mercury lamp (Eikousha EHB WF-100), set inside of the flask, through a Pyrex glass filter. Vigorous stirring continued under a nitrogen atmosphere.

References: K. Siago, M. Sukegawa, Y. Maekawa, M. Hasegawa, *Bull. Chem. Soc. Jpn.*, **68**, 2355 (1995).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: (Z,Z)-2,4-hexadienedicarboxylate, topochemical 1,4-polymerization, photoirradiation



Experimental procedures:

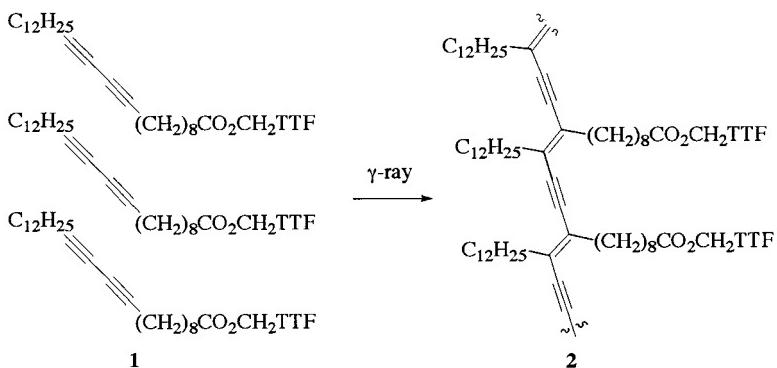
Photopolymerization of the crystals was carried out in a sealed Pyrex ampule under irradiation of UV light using a high-pressure mercury lamp (Toshiba SHL-100-2, 100 W) at a distance of 10 cm. A typical polymerization procedure is described below. Monomer diethyl *cis,cis*-muconate **1** (200 mg, 1.0 mmol) was placed in an ample, which was then evacuated on a vacuum line. After irradiation, polymer was isolated by removal of the unreacted monomer with chloroform (20 mL) for 5–10 h at room temperature. Photopolymerization was also carried out by direct exposure to sunlight.

References: A. Matsumoto, K. Yokoi, S. Aoki, K. Tashiro, T. Kamae, M. Kobayashi, *Macromolecules*, **31**, 2129 (1998).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: diacetylene, tetrathiafulvalene, γ -ray irradiation, polydiacetylene



Experimental procedures:

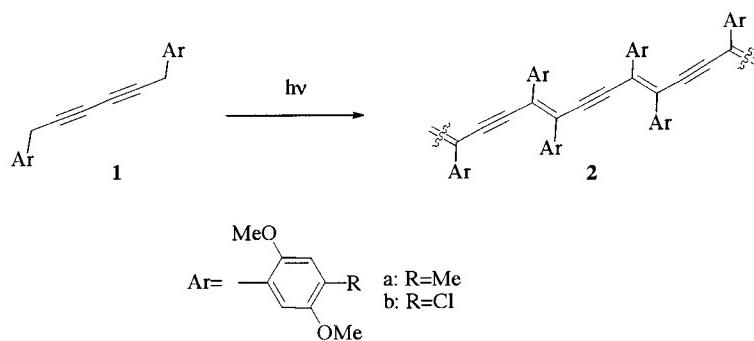
The color of the burk crystals of monomer **1** changed to dark blue from light yellow after exposure to UV with a low-pressure mercury lamp (4 W) or ^{60}Co γ -ray irradiation.

References: S. Shimada, A. Masaki, K. Hayamizu, H. Matsuda, S. Okada, H. Nakanishi, *Chem. Commun.*, 1421 (1997).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 1,6-bis(2,5-dimethoxyphenyl)hexa-2,4-diyne, photopolymerization, diacetylene, polydiacetylene

**Experimental procedures:**

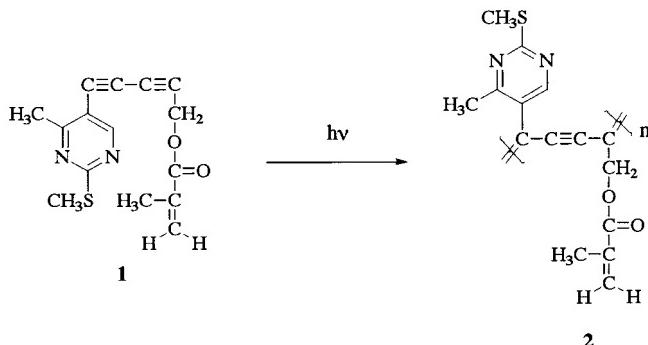
A sample of 10.2 mg (24.4 mmol) of powdered **1b** was irradiated with UV light for 6 h. The resulting violet solid was then extracted with dichloromethane for 4 h to remove unreacted monomer. Drying in *vacuo* to constant mass gave 1.8 mg (18%) of **2b** as a light-violet solid, mp >320 °C.

References: H. Irngartiger, M. Skipinski, *Eur. J. Org. Chem.*, **917** (1999); H. Irngartiger, M. Skipinski, *Tetrahedron*, **56**, 6781 (2000).

Type of reaction: C–C bond formation

Reaction condition: solid-state

Keywords: 5-(2-methylthio-4-methylpyrimidin-5-yl)penta-2,4-diyn-1-ol, polymerization



Experimental procedures:

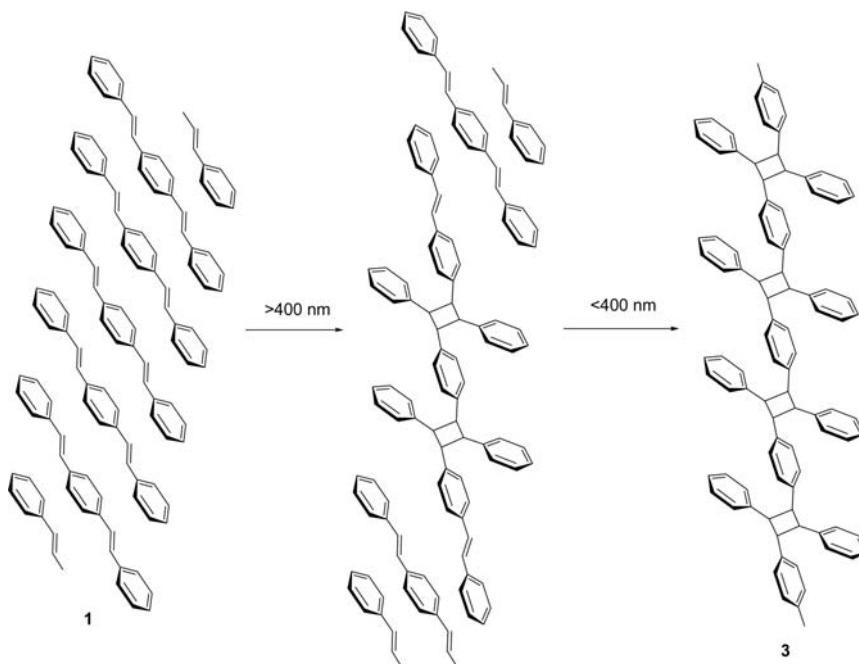
The monomer **1** was polymerized by heating the crystals in a vacuum vessel below the melting point or by γ -ray or UV irradiation of the crystals at room temperature. ^{60}Co γ -ray irradiation with a dose rate of 0.1 Mrad h^{-1} or a high-pressure mercury lamp (200 W) without filter was used as the radiation sources for the polymerization; the conversion ratio was determined by extraction of residual monomer with ethanol. A comparison of the polymerization rates indicates that ^{60}C γ -ray irradiation is much more efficient than UV irradiation in inducing polymerization.

References: J.-H. Wang, Y.-Q. Shen, C.-X. Yu, J.-H. Si, *J. Chem. Soc., Perkin Trans. 1*, 1455 (2000).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: 2,5-distyrylpyrazine, topochemical reaction



Experimental procedures:

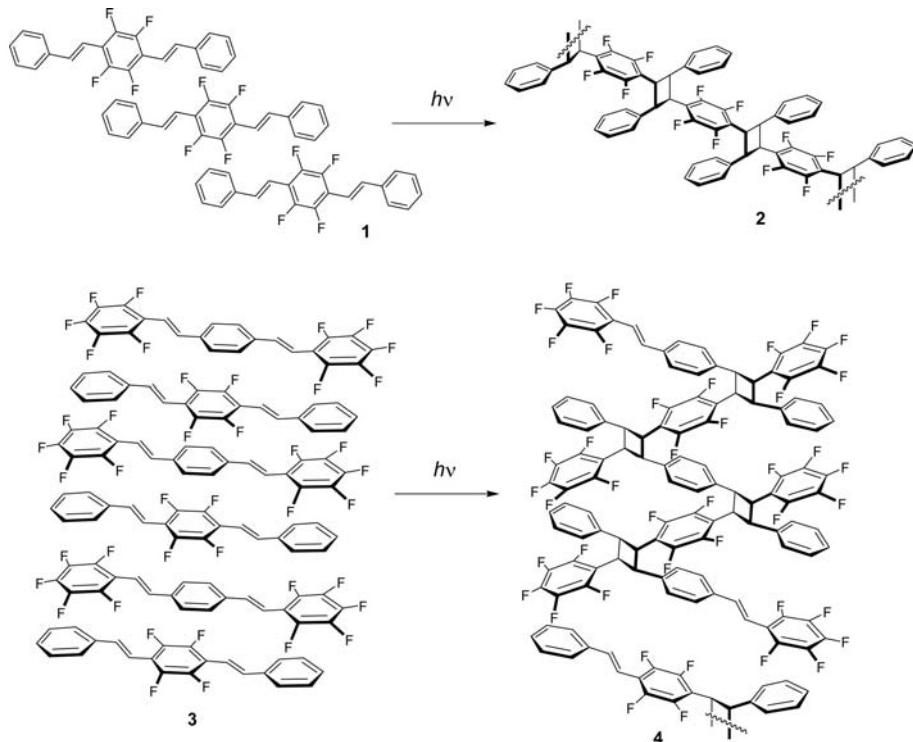
Partially oligomerized crystals were obtained by irradiation of monomer crystals with monochromatized light (490 nm) from a 1000-W quartz halogen lamp. Crystals were continuously rotated perpendicular to the *a* crystallographic axis to compensate for anisotropies arising from crystal optics, polarization effects due to the monochromator, and inhomogeneities in the light source. The extent of oligomerization was determined by dissolving a crystal in a 3-nitrobenzyl alcohol matrix and analyzing fast atom bombardment mass spectrometry data with monomeric DSP as the standard.

References: J.J. Stezowski, N.M. Peachey, P. Goebel, C.J. Eckhardt, *J. Am. Chem. Soc.*, **115**, 6499 (1993).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: [2+2]photodimerization, phenyl-perfluorophenyl stacking interaction



Experimental procedures:

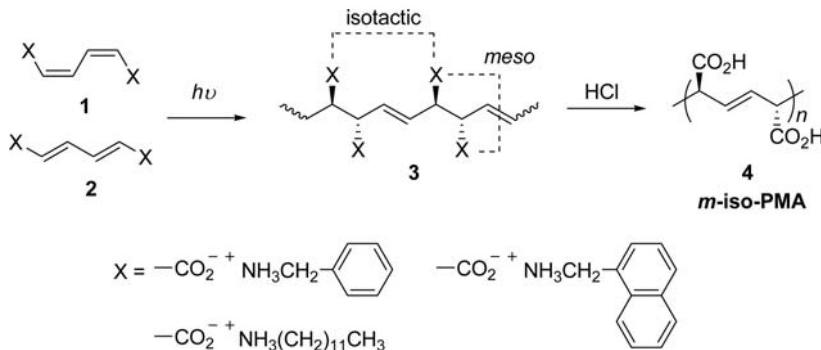
Crystals of **1** (43 mg) were placed in a Pyrex reaction tube under argon and photolyzed for 20 h at ambient temperature. The resulting white powder was extracted with 100 mL of refluxing toluene, yielding a soluble material upon filtration (6.5 mg, 15%).

References: G. W. Coates, A. R. Dunn, L. M. Henling, J. W. Ziller, E. B. Lobkovsky, R. H. Grubbs, *J. Am. Chem. Soc.*, **120**, 3641 (1998).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: intercalation, poly(muconic acid)



Experimental procedures:

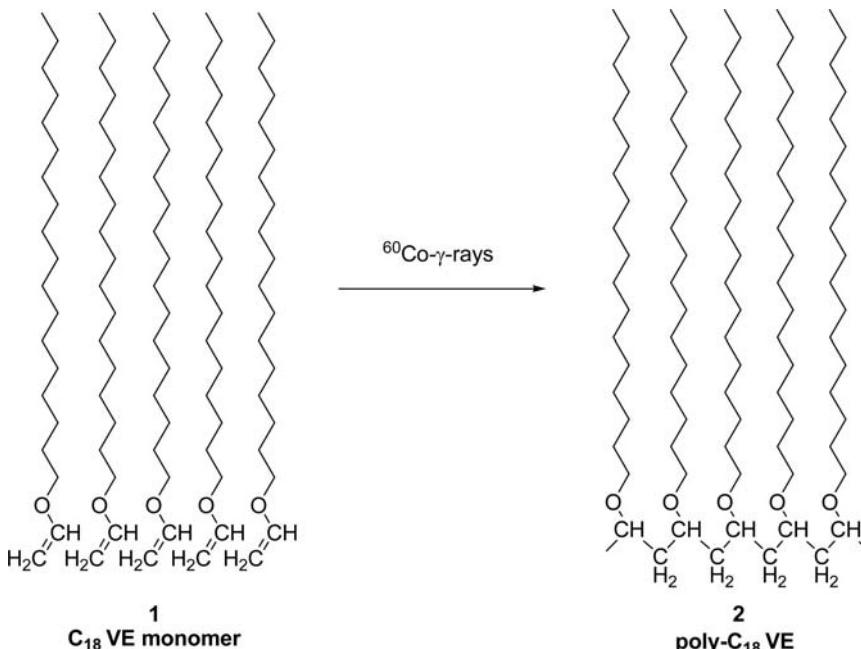
The photopolymerization of di(dodecylammonium) (*Z,Z*)-muconate (7.78 g, 15.2 mmol) was carried out in the crystalline state under UV irradiation using a high-pressure mercury lamp (Toshiba SHL-100-2, 100 W) at a distance of 10 cm. The resultant polymer was isolated by removing the unreacted monomer with methanol. Polymer yield: 80%.

References: S. Oshita, A. Matsumoto, *Chem. Eur. J.*, **12**, 2139 (2006); A. Matsumoto, T. Tanaka, K. Oka, *Synthesis*, **9**, 1479 (2005); S. Nagahama, T. Tanaka, A. Matsumoto, *Angew. Chem. Int. Ed.*, **43**, 3811 (2004); S. Nagahama, A. Matsumoto, *J. Am. Chem. Soc.*, **123**, 12176 (2001); K. Tashiro, A. N. Zadorin, S. Saragai, T. Kamae, A. Matsumoto, K. Yokoi, S. Aoki, *Macromolecules*, **32**, 7946 (1999).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: γ -ray irradiation, 1-octadecyl vinyl ether



Experimental procedures:

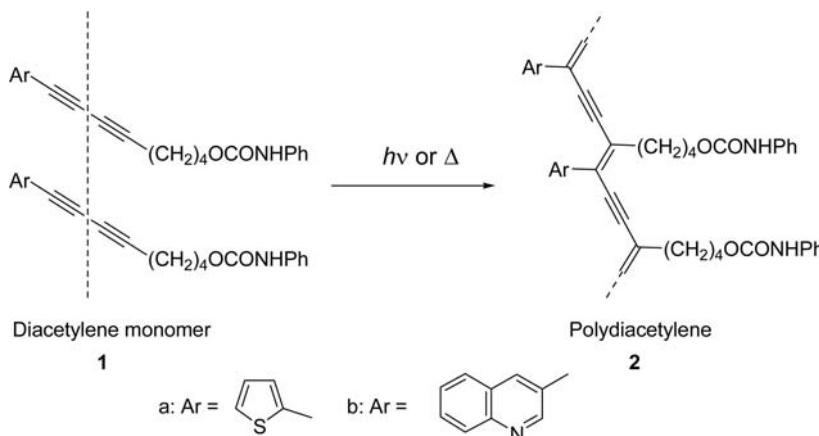
The monomer sample (ca. 1.5 mg) was sealed in a Pyrex tube (inside diameter: 10 mm) in a vacuum or nitrogen atmosphere and irradiated with ^{60}Co γ rays (1.0 to 3.0 Mrad) in liquid N₂ at -196 °C. The γ -ray irradiation was carried out at the Japan Atomic Energy Institute at Takasaki. Solid-state postpolymerization was carried out at various temperatures (30, 25, 20, 10, 5, 0, -10, -20, and -83.6 °C). The samples, polymerized for various time periods (0.5, 1, 2, 3, 6, 12, and 24 h), were dissolved in 10 ml of THF, and then the solutions were poured into 100 ml of cold acetone to separate polymer and monomer. The precipitate of the polymer was isolated on a glass filter, and the conversions were determined from the weights of polymer obtained after drying under vacuum at room temperature.

References: A. Fujimori, H. Saitoh, Y. Shibasaki, *J. Poly. Science; Part A, Poly. Chem.*, **37**, 3845 (1999).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: diacetylene, polydiacetylene



Experimental procedures:

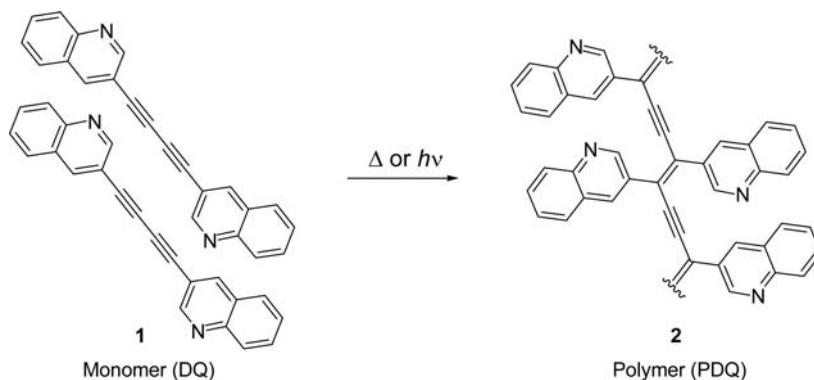
Solid state polymerization of the monomers was performed by UV or γ -radiation. ^{60}Co γ -radiation dosage was used to convert bulk monomers in evacuated and sealed glass tubes to their respective polymers. To calculate the rate of polymerization, various dosages were used for a given monomer and the conversion to polymer was determined by extracting the reaction mixture with hot chloroform and weighing the undissolved polymer portions. The percentage polymer conversion was calculated by comparing the weight of the sample before and after extraction.

References: A. Sarkar, S. Okada, H. Nakanishi, H. Matsuda, *Macromolecules*, **31**, 9174 (1998).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: 1,3-bis(3-quinolyl)-1,4-butadiyne, polydiacetylene



Experimental procedures:

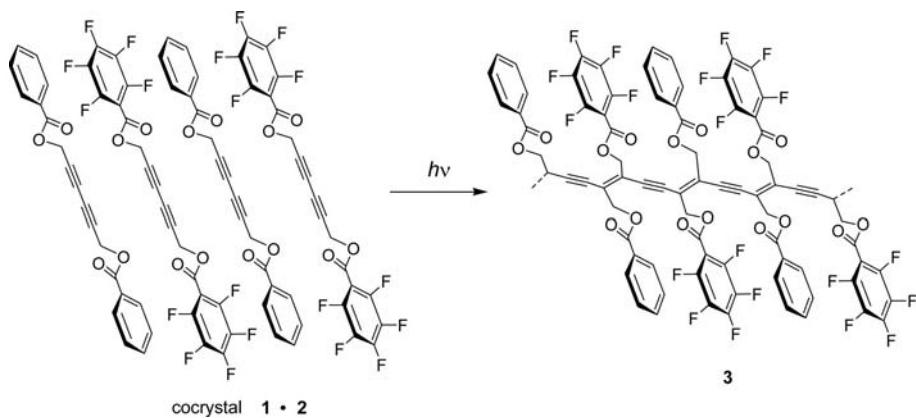
Partially polymerized samples of DQ bulk crystals were obtained by UV irradiation from an 8-W UV lamp at 254 nm or thermal annealing at 190 °C in an ambient atmosphere. Polymer of DQ (PDQ) was obtained by extracting the unreacted monomer from the partially polymerized DQ using chloroform as the monomer solvent.

References: T. Li, S. Okada, H. Umezawa, H. Kasai, H. Nakanishi, S.S. Talwar, T. Kimura, H. Matsuda, *Polymer Bulletin*, **57**, 737 (2006).

Type of reaction: Polymerization

Reaction condition: solid-state

Keywords: diacetylene copolymer, 2,4-hexadiynylene dibenzoate



Experimental procedures:

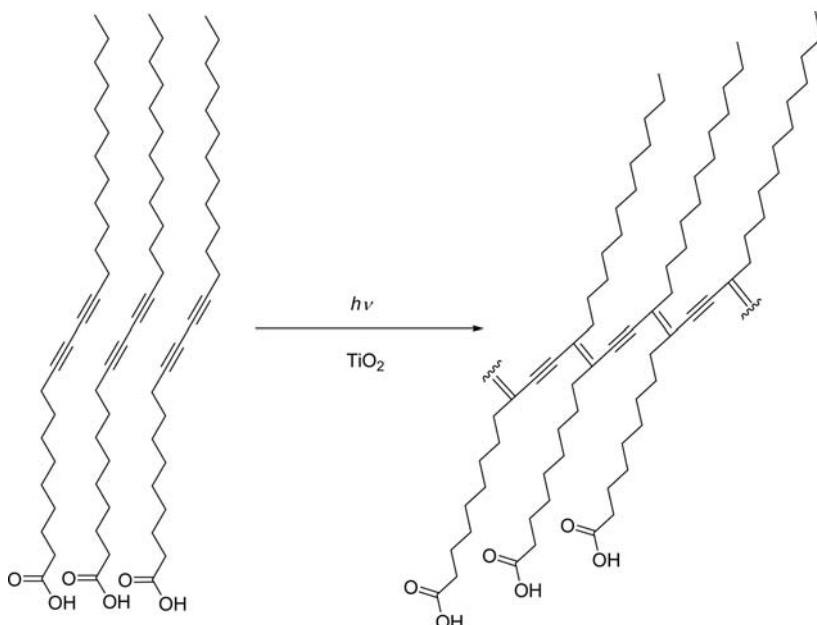
UV irradiation of the cocrystals **1–2** led to their conversion into a deep red, insoluble material. After 18 h of irradiation, the pure copolymer **3** was obtained in 35% yield after extraction of residual monomer with DCM.

References: R. Xu, V. Gramlich, H. Frauenrath, *J. Am. Chem. Soc.*, **128**, 5541 (2006).

Type of reaction: polymerization

Reaction condition: solid-state

Keywords: diacetylene, nanocrystalline TiO₂, 10,12-pentacosadiynoic acid

**Experimental procedures:**

Several 3-μm thick nanoporous TiO₂ films (Degussa P25) were spin-coated onto fluorine-doped tin oxide-coated glass substrates. After sintering at 450 °C for 30 min, the diacetylene monomer, 10,12-pentacosadiynoic acid (DA-3261; GFS Chemicals), was added to the nanoporous TiO₂ films by solution drop-casting from tetrahydrofuran (THF; 0.05 M). The polymerization was carried out by exposing the DA-3261/TiO₂ nanocomposites to fluorescent lamps (Sylvania Octron 4100K; 0.3 mW cm⁻²) and a series of monochromatic light within the fluorescent lighting spectrum.

References: Y. Wang, L. Li, K. Yang, L.A. Samuelson, J. Kumar, *J. Am. Chem. Soc.*, **129**, 7238 (2007).

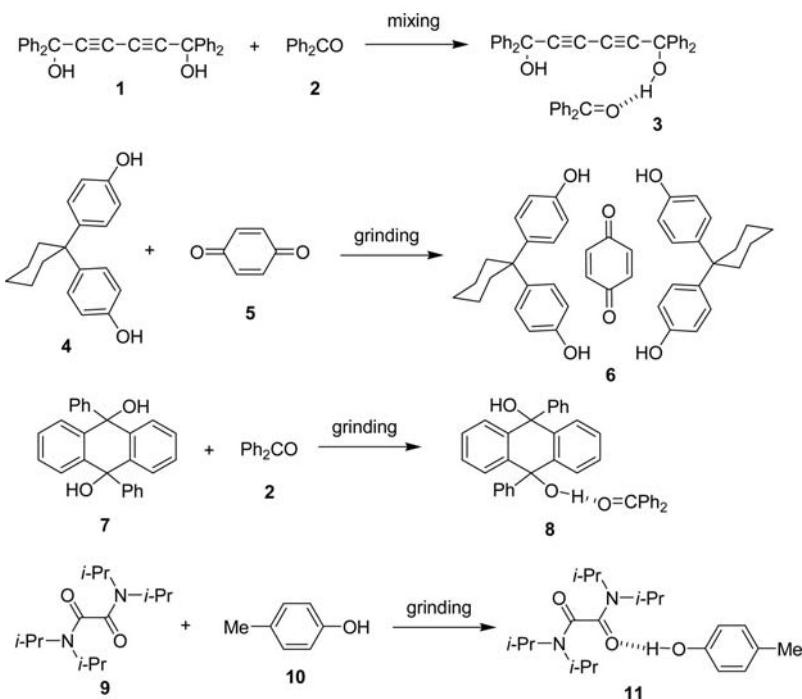
15 Supramolecular Complexation

15.1 Solvent-Free Supramolecular Complexation

Type of reaction: supramolecular complexation

Reaction condition: solid-state

Keywords: 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol, benzophenone



Experimental procedures:

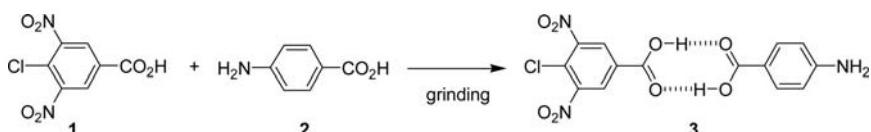
When a mixture of finely powdered 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol **1** and an equimolar amount of finely powdered benzophenone **2** was agitated using a test-tube shaker for 0.2 h at room temp., a 1:1 complex **3** involving these two compounds was formed.

References: F. Toda, K. Tanaka, A. Sekikawa, *J. Chem. Soc., Chem. Commun.*, 279 (1987); D. R. Bond, L. Johnson, L. R. Nassimbeni, F. Toda, *J. Solid State Chem.*, **92**, 68 (1991).

Type of reaction: supramolecular complexation

Reaction condition: solid-solid

Keywords: 4-chloro-3,5-dinitrobenzoic acid, 4-aminobenzoic acid



Experimental procedures:

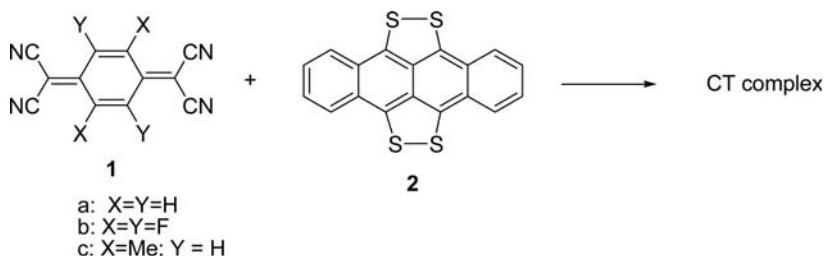
Experimental procedures. Co-crystal **3** was prepared either in solution, by rapid cooling of an equimolar solution of **1** and **2** in ethanol-methanol, or in the solid state by grinding **1** and **2** in a mill for about 20 min at room temperature.

References: M.C. Etter, G.M. Frankenbach, J. Bernstein, *Tetrahedron Lett.*, **30**, 3617 (1989).

Type of reaction: supramolecular complexation

Reaction condition: solid-solid

Keywords: charge-transfer complex, tetracyanoquinodimethane, tetrathianaphthalene



Experimental procedures:

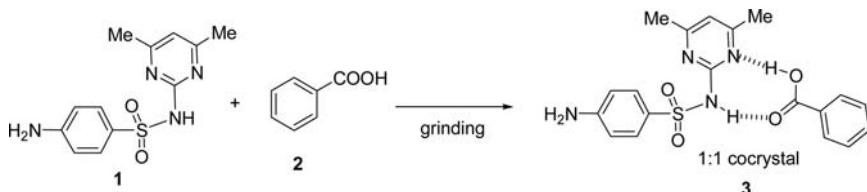
When a mixture of yellow crystals of **1a** (0.204 g, 1 mmol) and orange crystals of **2** (0.204 g, 1 mmol) was ground occasionally for 1 h by using an agate mortar and pestle, the CT complex of **2-1a** was formed as a black crystalline powder.

References: F. Toda, H. Miyamoto, *Chem. Lett.*, 861 (1995).

Type of reaction: supramolecular complexation

Reaction condition: solid-solid

Keywords: cocrystal, sulfonamide, carboxylic acid



Experimental procedures:

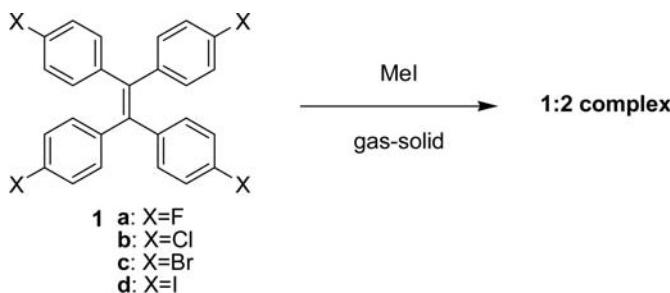
Sulfonamide **1** (140 mg, 0.5 mmol) and benzoic acid **2** (61 mg, 0.5 mmol) were mixed and ground manually in a mortar and pestle for 4 min. The mixture was then ground for 3 min in a Grindex ball grinder using a 12 mm iron ball (8.34 g) in a stainless steel cylinder of internal diameter 14 mm and length 35 mm.

References: M.R. Caira, L.R. Nassimbeni, A.F. Wildervanck, *J. Chem. Soc. Perkin Trans. 2*, 2213 (1995).

Type of reaction: supramolecular complexation

Reaction condition: gas-solid

Keywords: tetra(*p*-halophenyl)ethylene, methyl iodide



Experimental procedures:

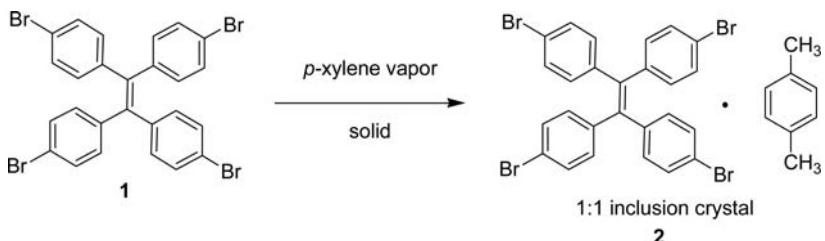
When exposed to methyl iodide vapor at room temperature for 5 h, the crystalline powder of **1d** was changed into the 1:2 inclusion complex of **1d** with methyl iodide.

References: K. Tanaka, D. Fujimoto, F. Toda, *Tetrahedron Lett.*, **41**, 6095 (2000).

Type of reaction: supramolecular complexation

Reaction condition: gas-solid

Keywords: tetra(*p*-bromophenyl)ethylene, inclusion crystal



Experimental procedures:

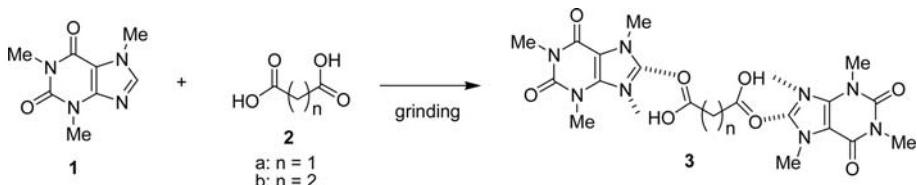
When exposed to *p*-xylene vapor at room temperature for 24 h, a single crystal of pure 1 prepared by recrystallization from *m*-xylene was gradually changed into the chiral polycrystalline 1:1 inclusion complex 2 of 1 with *p*-xylene.

References: K. Tanaka, D. Fujimoto, T. Oeser, H. Irngartinger, F. Toda, *Chem. Commun.*, 413 (2000).

Type of reaction: supramolecular complexation

Reaction condition: solid-solid

Keywords: caffeine, dicarboxylic acid, cocrystal



Experimental procedures:

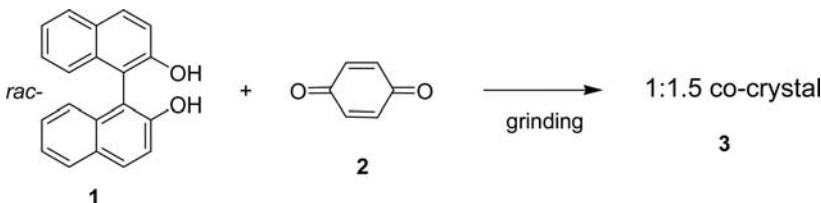
Cocrystals 3 were prepared by grinding β -caffeine 1 (0.38 g, 2.0 mmol) and oxalic acid 2b (0.89 g, 0.5 equiv.) for 60 min.

References: A.V. Trask, W.D.S. Motherwell, W. Jones, *Cryst. Growth. Des.*, 5, 1013 (2005).

Type of reaction: supramolecular complexation

Reaction condition: solid-solid

Keywords: *rac*-bis- β -naphthol, benzoquinone, cocrystal



Experimental procedures:

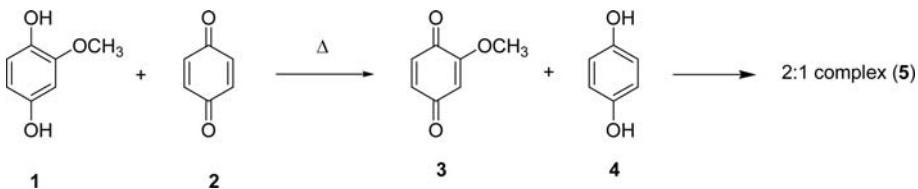
On grinding white racemic crystals of bis- β -naphthol **1** and yellow benzoquinone in an agate mortar in a ratio of 1:2.5, the color of the powder changed progressively with time from very pale yellow to pink and eventually to strong red.

References: R. Kuroda, Y. Imai, N. Tajima, *Chem. Commun.*, 2848 (2002); Y. Imai, N. Tajima, T. Sato, R. Kuroda, *Org. Lett.*, **8**, 2941 (2006).

Type of reaction: supramolecular complexation

Reaction condition: solvent-free

Keywords: quinhydrone, 2-methoxyhydroquinone, benzoquinone



Experimental procedures:

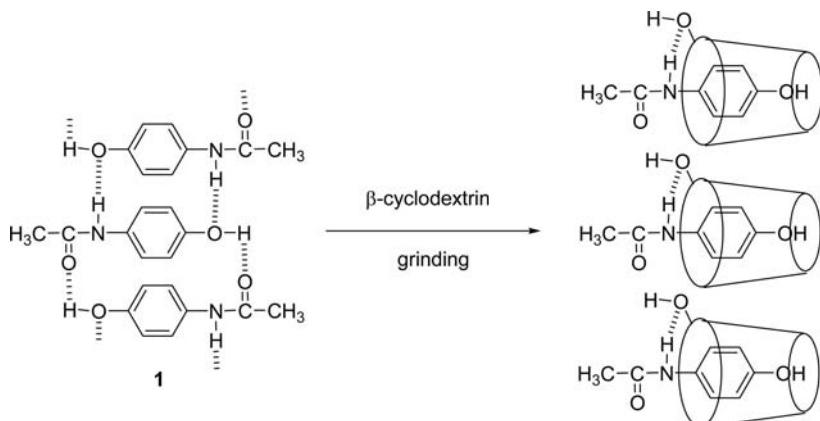
A Schlenk tube containing a mixture of **1** (50 mg, 0.35 mmol) and **2** (50 mg, 0.46 mmol) was purged under argon, evacuated under a primary vacuum and then closed. The tube was heated in a home-made vertical oven from room temperature to 100 °C for 13 h. Black needles, 2 cm in length, were formed 2 cm above the oven. **5**: mp 136 °C (dec.).

References: M. Bouvet, B. Malézieux, P. Herson, *Chem. Commun.*, 1751 (2006).

Type of reaction: supramolecular complexation

Reaction condition: solid-solid

Keywords: acetaminophen, β -cyclodextrin, mechanical grinding



Experimental procedures:

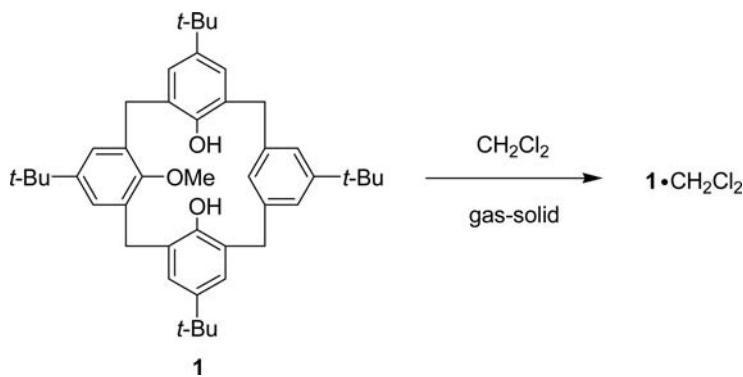
The ground mixtures of acetaminophen and α - or β -cyclodextrin in a 1:1 molar ratio were prepared by grinding the materials in a ceramic ball mill for 24 h. During the grinding process, samples were withdrawn at prescribed intervals (0, 0.5, 1.0, 3.0, 5.0, 7.0 and 24 h) for further examination.

References: S. Lin, C. Lee, *J. Incl. Phenom. Mol. Recog.*, **7**, 477 (1989).

Type of reaction: supramolecular complexation

Reaction condition: gas-solid

Keywords: monodeoxycalix[4]arene, apo-host



Experimental procedures:

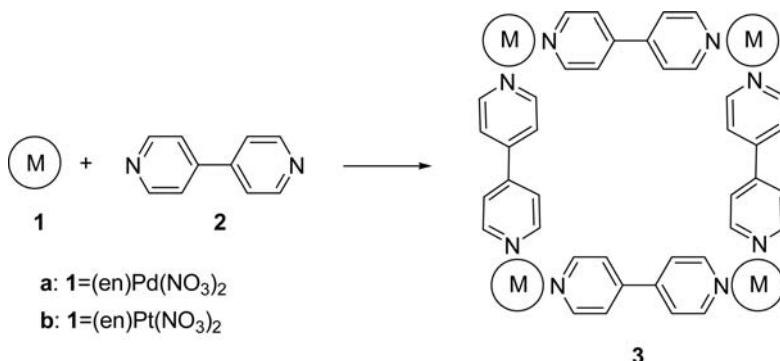
When exposed into the gaseous guest molecules, apo-hosts absorb the guest to give 1:1 host/guest complexes.

References: M. Hirakata, K. Yoshimura, S. Usui, K. Nishimoto, Y. Fukazawa, *Tetrahedron Lett.*, **43**, 1859 (2002).

Type of reaction: supramolecular complexation

Reaction condition: solvent-free

Keywords: self-assembly, 4,4'-bipyridine, palladium complex

**Experimental procedures:**

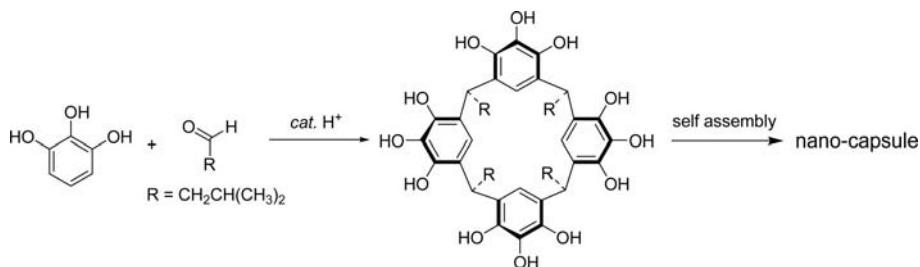
A powdered mixture of **1b** and **2** in a 1:1 ratio was ground in a mortar with a pestle in the ambient atmosphere. The mixture became gummy immediately. After 10 min, the ^1H NMR spectrum of the mixture in D_2O exhibited complete consumption of the starting materials and formation of **3b** together with a small amount of other species that could be attributed to linearly assembled oligomers. Reprecipitation of the mixture from water-ethanol furnished a 76% yield of **3b** whose spectral data were fully consistent with that reported.

References: A. Orita, L. Jiang, T. Nakano, N. Ma, J. Otera, *Chem. Commun.*, 1362 (2002).

Type of reaction: supramolecular complexation

Reaction condition: solid-state

Keywords: pyrogallo[4]arene, nano-capsule

**Experimental procedures:**

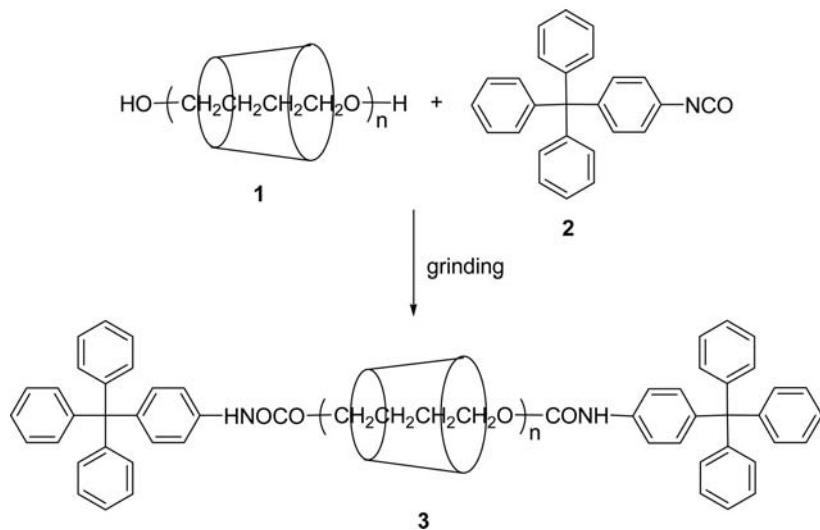
Isovaleraldehyde (0.89 ml, 7.9 mmol) was added dropwise to a fine dispersion of pyrogallol (1.00 g, 7.9 mmol) and a catalytic amount of solid *p*-toluenesulfonic acid (50 mg, 0.3 mmol) with constant grinding using a mortar and pestle. The condensation reaction yielded a bright white solid within 2 min of grinding. This solid was easily milled to a fine, yellow powder upon further aggregation.

References: J. Antesberger, G. W. V. Cave, M. C. Ferrarelli, M. W. Heaven, C. L. Raston, J. L. Atwood, *Chem. Commun.*, 892 (2005).

Type of reaction: supramolecular complexation

Reaction condition: solid-solid

Keywords: pseudopolyrotaxane, 4-triphenyl isocyanate, permethylated α -cyclo-dextrin



Experimental procedures:

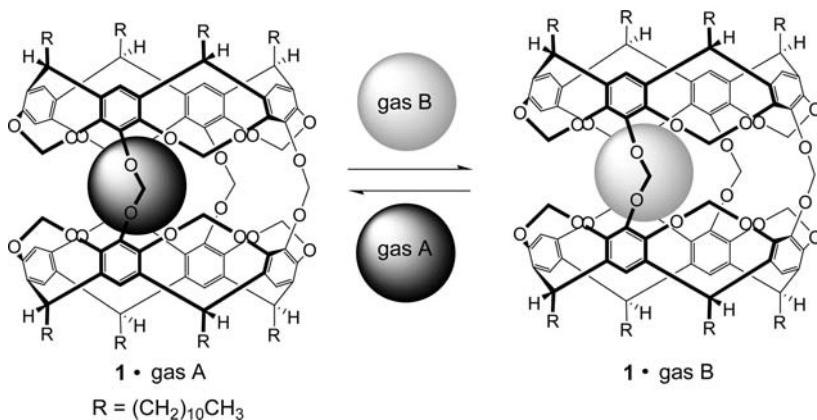
A mixture of **1**, **2** and dibutyltin dilaurate (7 mol%) was well ground in an agate mortar at room temperature. From the mixture after 30 min grinding, polyrotaxane **3** was isolated in 24% yield as the ether- and methanol-insoluble part.

References: N. Kihara, K. Hinoue, T. Takata, *Macromolecules*, **38**, 223 (2005).

Type of reaction: supramolecular complexation

Reaction condition: solid-state

Keywords: hemicarcerand, gas-solid reaction, hemicarceplex

**Experimental procedures:**

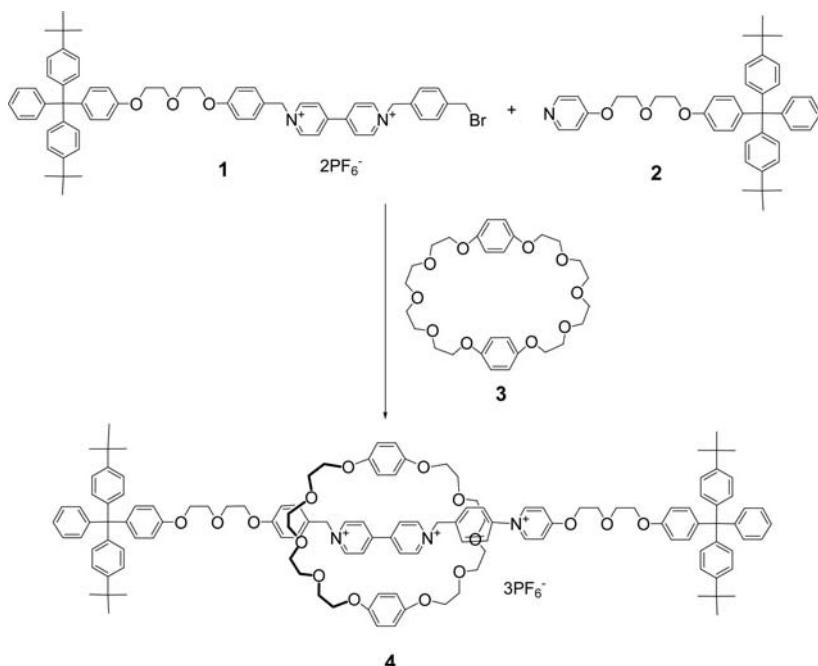
Upon flushing the powder containing **1** and **1** (N_2) with CO_2 or N_2O for 1 h, hemicarceplexes **1** (CO_2) or **1** (N_2O) were obtained quantitatively. Upon exposure to a stream of H_2 , solid hemicarceplex **1** (CO_2) completely loses the CO_2 , and the NMR spectrum of the thus obtained solid is similar to the spectrum with H_2 reported in solution.

References: A. V. Leontiev, D. M. Rudkevich, *Chem. Commun.*, 1468 (2004).

Type of reaction: Supramolecular Complexation

Reaction condition: solvent-free

Keywords: [2]rotaxan



Experimental procedures:

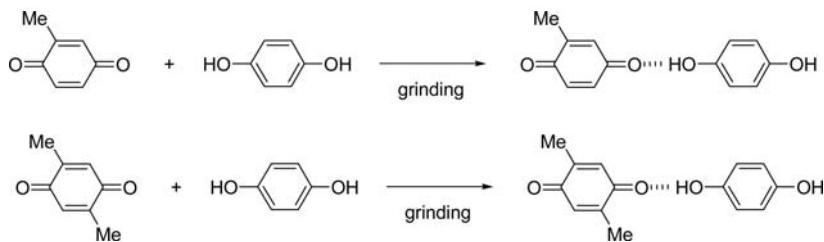
A mixture of **1** (37 mg, 0.03 mmol), **2** (36 mg, 0.06 mmol) and **3** (32 mg, 0.06 mmol) was dissolved in acetone (0.1 mL) and dichloromethane (0.1 mL) in a 50-mL flask. The resulting red solution was evaporated *in vacuo*, whereupon a film developed on the surface of the flask. After 5 min, the evaporation was stopped and the film was left standing in the open air at ambient temperature for 4 h. The mixture was dissolved in acetone (10 mL) and H_2O (2 mL). NH_4PF_6 (98 mg, 0.6 mmol) was added to the resulting solution. The acetone was evaporated from this solution, and the resulting H_2O suspension was filtered. The solid product thus obtained was dried *in vacuo*. Column chromatography of this mixture on silica gel (70:16:11:3 MeOH/ CH_2Cl_2 /MeNO₂/NH₄Cl (2N) furnished **4** (56 mg, 79%).

References: A. Orita, J. Okano, Y. Tawa, L. Jiang, J. Otera, *Angew. Chem. Int. Ed.*, **43**, 3724 (2004).

Type of reaction: supramolecular complexation

Reaction condition: solid-state

Keywords: quinine, hydroquinone, quinhydrone

**Experimental procedures:**

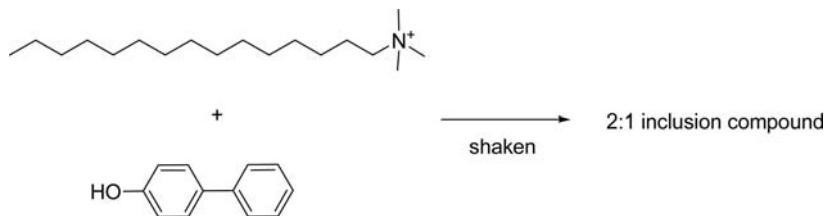
An agate mortar and pestle were used to grind the appropriate amounts (typically 10^{-3} mol) of the quinine and hydroquinone, weighed to ± 0.1 mg, until there was no further visible change and then for an additional 5 min. In no case was any liquid detectable.

References: A.O. Patil, D.Y. Curtin, I.C. Paul, *J. Am. Chem. Soc.*, **106**, 348 (1984).

Type of reaction: supramolecular complexation

Reaction condition: solid-solid

Keywords: tetraalkylammonium salts, phenol, inclusion compound

**Experimental procedures:**

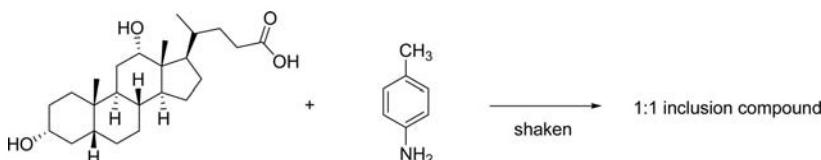
The powdered solids of host and guest were shaken for 1 min and kept at room temperature for 6 h to afford the 2:1 inclusion compound.

References: F. Toda, K. Tanaka, T. Okada, S.A. Bourne, L.R. Nassimbeni, *Supramol. Chem.*, **3**, 291 (1994).

Type of reaction: supramolecular complexation

Reaction condition: solid-solid

Keywords: cholic acid, *p*-toluidine, inclusion compound



Experimental procedures:

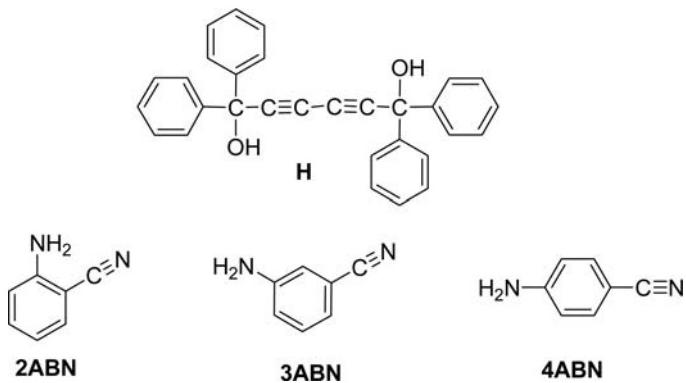
Dried, sieved cholic acid (CA, particle size = 212–250 mm) and finely ground *p*-toluidine (recrystallized) were combined in a 1:10 molar ratio in a round-bottomed flask and shaken continuously to ensure constant mixing of the components. Samples were periodically removed from the reaction vessel and immediately washed with copious amounts of diethyl ether to remove all unreacted *p*-toluidine, (neither CA nor the CA· *p*-toluidine inclusion compound is soluble in ether).

References: J. L. Scott, *J. Chem. Crystallogr.*, **26**, 185 (1996).

Type of reaction: supramolecular complexation

Reaction condition: solid-state

Keywords: 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol, aminobenzonitrile



Experimental procedures:

In each case grinding for 20 min at room temperature yielded a product that had the same structure as that found in the host–guest compound grown as single crystals from solution. This was checked by analysis of the measured X-ray pow-

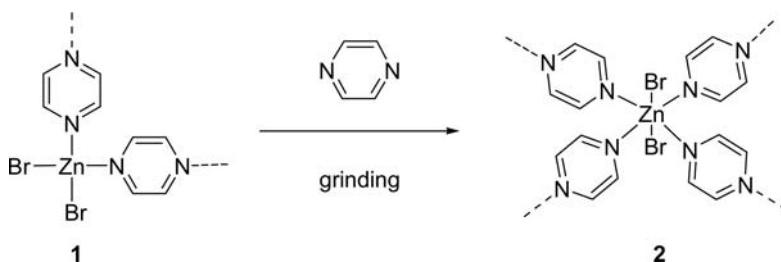
der diffraction pattern of the ground product, which was compared with the calculated pattern derived from the single-crystal structure.

References: M. R. Caira, L. R. Nassimbeni, F. Toda, D. Vujovic, *J. Am. Chem. Soc.*, **122**, 9367 (2000).

Type of reaction: supramolecular complexation

Reaction condition: solid-state

Keywords: coordination polymer, zinc (II) bromide, pyrazine



Experimental procedures:

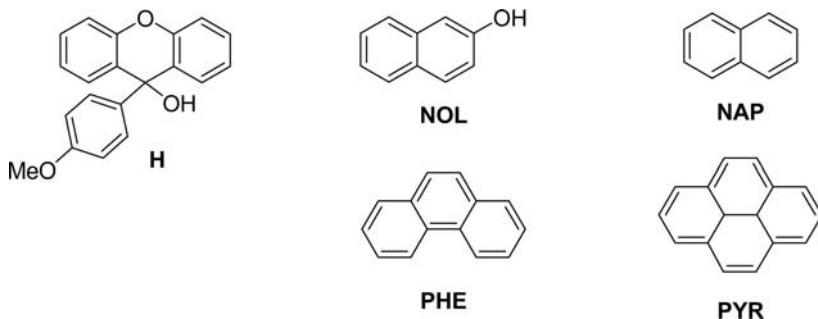
Pyrazine (0.039 g, 0.49 mmol) was added to powdered **1** (0.150 g, 0.49 mmol). The mixture was shaken in a WIG-L-BUG for 30 min at room temperature. The resulting compound was analyzed using XPRD.

References: S.A Bourne, M. Kilkenny, L.R. Nassimbeni, *J. Chem. Soc., Dalton Trans.*, 1176 (2001).

Type of reaction: supramolecular complexation

Reaction condition: solid-state

Keywords: 9-(4-methoxyphenyl)-9H-xanthen-9-ol, clathrate, 2-naphthol



Experimental procedures:

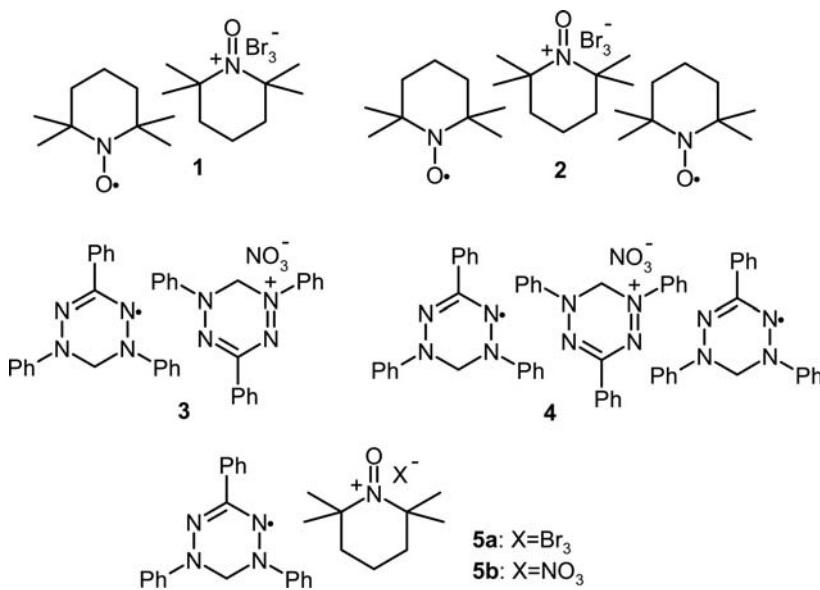
Grinding was carried out over a period of 2 h at 298 K. There was a good match between the peaks of the diffraction patterns of the product powder and the co-ordinates of the host (**H**) $^{1/2}$ β -naphthol (**NOL**) structure.

References: E. Curtis, L.R. Nassimbeni, H. Su, J.H. Taljaard, *Cryst. Growth. Des.*, **6**, 2716 (2006).

Type of reaction: supramolecular complexation

Reaction condition: solid-state

Keywords: solid-solid reaction, ball milling, stable radicals, TEMPO, TEMPO-nitrosonium salts, TEMPO-nitrosonium salts, triphenylverdazylum salts

**Experimental procedure:**

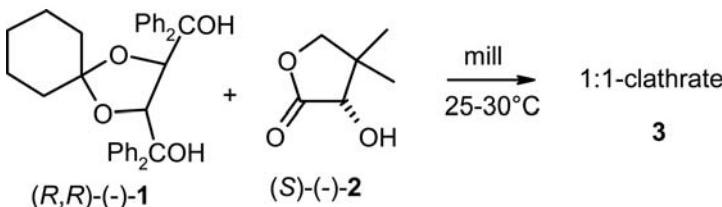
The complexes **1–5** were prepared by stoichiometric milling in a Teflon beaker with agate balls for 30 min at 20 °C. All exhibited distinct melting points and distinct antiferromagnetic properties.

References: S. Nakatsuji, A. Takai, M. Mizumoto, H. Anzai, K. Nishikawa, Y. Morimoto, N. Yasuoka, J. Boy, G. Kaupp, *Mol. Cryst. Liq. Cryst.*, **334**, 177 (1999); G. Kaupp, *Top. Curr. Chem.*, **254**, 95 (2005).

Type of reaction: supramolecular complexation

Reaction condition: solid-state

Keywords: solid-solid reaction, ball milling, TADDOL, pantolactone, clathrate



Experimental procedure:

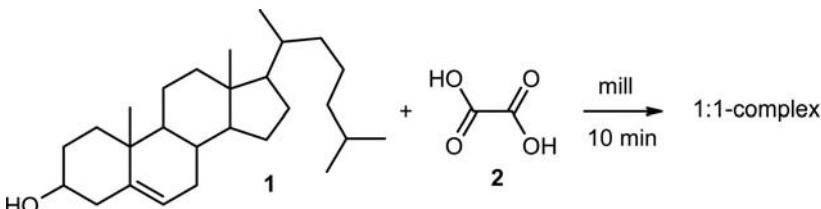
A stoichiometric mixture of **1** (2.00 mmol) and **2** (2.00 mmol) was ball-milled at 25–30 °C for 30 min to obtain the uniform clathrate **3**.

References: G. Kaupp, *Top. Curr. Chem.*, **254**, 95 (2005).

Type of reaction: supramolecular complexation

Reaction condition: solid-state

Keywords: solid-solid reaction, ball milling, cholesterol, oxalic acid, complex



Experimental procedure:

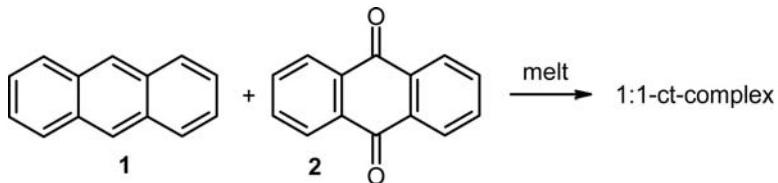
A stoichiometric mixture of **1** (1.00 mmol) and **2** (1.00 mmol) was ball-milled at 25 °C for 10 min to obtain the uniform 1:1-complex with distinct IR spectrum.

References: G. Kaupp, Waste-free synthesis and production all across chemistry with the benefit of self-assembled crystal packings, *J. Phys. Org. Chem.*, **2008**, 21, DOI 10.1002/poc1340; G. Kaupp, *Top. Curr. Chem.*, **254**, 95 (2005).

Type of reaction: supramolecular complexation

Reaction condition: melt reaction

Keywords: anthracene, anthraquinone, melt, charge transfer complex

**Experimental procedure:**

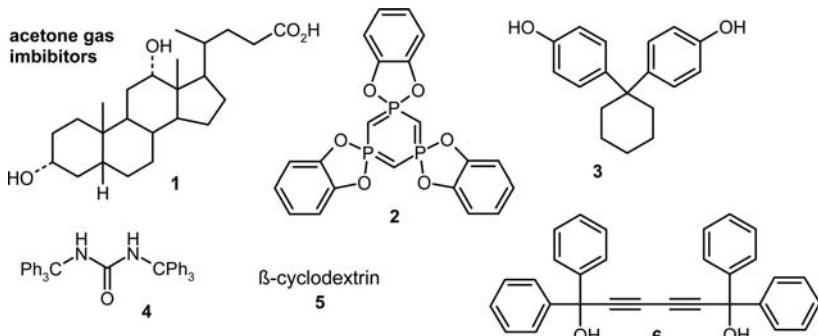
A stoichiometric mixture of **1** (1.00 mmol) and **2** (1.00 mmol) was completely melted in a test tube and rapidly cooled to room temperature to obtain the deep brown charge transfer complex with distinct IR spectrum. This crystalline complex separated into the components upon standing for several months at room temperature. It did not form upon milling or in solution.

References: G. Kaupp, A. Herrmann, *J. Phys. Org. Chem.*, **10**, 675 (1997); G. Kaupp, *Top. Curr. Chem.*, **254**, 95 (2005).

Type of reaction: supramolecular complexation

Reaction condition: solid-state

Keywords: gas-solid reaction, acetone gas imbibition, inclusion compounds, desorption temperatures



Gas-solid imbibitions of acetone

Host	Acetone/Host (imbibed)	$\nu_{(C=O)}$ [cm $^{-1}$]	Desorption tem- perature [$^{\circ}$ C]	Acetone/Host (crystallized)
1	—	—	—	0.58 ^[a]
2	0.48	1716	146	0.20
3	0.61	1701	63	0.58
4	0.97	1711	121	0.76
5	2.56	1705	143	1.55
6	2.0	1702	70	2.0

[a] E. Weber, M. Czugler, *Top. Curr. Chem.*, **149**, 45 (1988).

Experimental procedure:

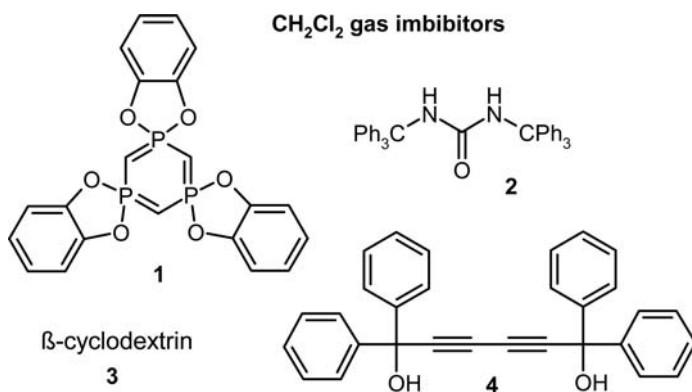
The ground host (2.00 mmol) was evacuated in a 250-mL flask that was connected at a vacuum line to a second 250-mL flask containing 2 mmol (for **4**: 3 mmol; for **5** and **6**: 6 mmol) acetone. After 1 h at room temperature excess gas was condensed into flask 2 and the inclusion product evacuated for 1 h at 5×10^{-4} Torr. The table gives the molar ratio, the C=O IR frequency of the included acetone, the desorption temperature (from TGA experiments), and the comparison with the molar ratio that was obtained from crystallization of the complex in liquid acetone. Below the imbibition ratios the acetone gas was completely taken up within detection limits. Exhaust gases required column flow systems for removal of acetone as an inclusion compound.

References: G. Kaupp, U. Pogodda, J. Schmeyers, *Chem. Ber.* **127**, 2249 (1994); G. Kaupp, *Top. Curr. Chem.*, **254**, 95 (2005); there are also gas-solid imbibitions of hexane, heptane, cyclohexane, methylcyclohexane, benzene, toluene, dichloromethane, furan, tetrahydrofuran, dioxane, methyl *t*-butyl ether, ethyl acetate, methanol, ethanol and nitrogen dioxide.

Type of reaction: supramolecular complexation

Reaction condition: solid-state

Keywords: gas-solid reaction, dichloromethane gas imbibition, inclusion compounds, desorption temperature



Experimental procedure:

The ground host (2.00 mmol) was evacuated in a 250-mL flask that was connected at a vacuum line to a second 250-mL flask containing 2 mmol (for **1**, **2**) or 5 mmol (for **3**, **4**) dichloromethane. After 1 h at room temperature excess gas was condensed into flask 2 and the inclusion product evacuated for 1 h at 5×10^{-4} Torr.

The molar gas/solid imbibition ratios (from TGA experiments) and desorption temperatures were: for **1** 0.44 and 147 °C, for **2** 0.93 and 117 °C, for **3** 1.43 and 125 °C and for **4** 2.0 and 70 °C. Below the reported ratios the CH₂Cl₂ gas was completely taken up within detection limits. Exhaust gases required column flow systems for removal of dichloromethane as the inclusion compound.

References: G. Kaupp, *Top. Curr. Chem.*, **254**, 95 (2005); there also gas-solid imbibitions of hexane, heptane, cyclohexane, methylcyclohexane, benzene, toluene, acetone, furan, tetrahydrofuran, dioxane, methyl *t*-butyl ether, ethyl acetate, methanol, ethanol, nitrogen dioxide.

List of Journals

The following is a list of the journals scanned in the preparation of this volume. In most cases they were scanned from 1980 to 2007.

Adv. Synth. Catal.	J. Org. Chem.
Angew. Chem.	J. Organomet. Chem.
Angew. Chem. Int. Ed. Engl.	J. Photochem. Photobiol. A
Bull. Chem. Soc. Jpn.	J. Phys. Org. Chem.
Carbohydrate Res.	J. Poly. Science: Part A, Poly. Chem.
Chem. Ber.	J. Prakt. Chem.
Chem. Commun.	J. Solid State Chem.
Chem. Exp.	Liebigs Ann.
Chem. Lett.	Macromolecules
Chem. Eur. J.	Macromol. Chem. Phys.
Chem. Engin. Sci.	Mol. Cryst. Liq. Cryst.
Chem. Mater.	Monatsh. Chem.
Chemosphere	Mendeleev Commun.
Chemie Technik	Merck Spectrum
ChemSusChem	Mol. Cryst. Liq. Cryst.
Chirality	Nippon Kagaku Kaishi
CrystEngComm	Nature
Cryst. Growth Des.	New J. Chem.
Eur. J. Org. Chem.	Organometallics
Eur. Polym. J.	Org. Biomol. Chem.
Green Chem.	Org. Lett.
Heterocycles	Org. Process. Res. Dev.
Helv. Chim. Acta	Phosphorus, Sulfur and Silicon
Indian J. Chem. Sect. B	Polymer
J. Am. Chem. Soc.	Polymer Bulletin
J. Chem. Crystallogr.	Synlett
J. Chem. Soc., Dalton Trans.	Synthesis
J. Chem. Soc., Perkin Trans. 1	Supramol. Chem.
J. Chem. Soc., Perkin Trans. 2	Synth. Commun.
J. Chem. Res. (S)	Tetrahedron
J. Fluorine Chem.	Tetrahedron:Asym.
J. Incl. Phenom. Mol. Recog.	Tetrahedron Lett.
J. Mol. Cat.	Top. Curr. Chem.
J. Mol. Cat. A: Chemical	

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